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(54) Title: BIODEGRADABLE SHAPE MEMORY POLYMERS

(57) Abstract

Biodegradable shape memory polymer compositions, articles of manufacture thereof, and methods of preparation and use thereof are described. In one embodiment the compositions include at least one hard segment and at least one soft segment. The T_{trans} of the hard segment is preferably between –30 and 270 °C. At least one of the hard or soft segments can contain a cross–linkable group, and the segments can be linked by formation of an interpenetrating network or a semi–interpenetrating network, or by physical interactions of the segments. Objects can be formed into a given shape at a temperature above the T_{trans} of the hard segment, and cooled to a temperature below the T_{trans} of the soft segment. If the object is subsequently formed into a second shape, the object can return to its original shape by heating the object above the T_{trans} of the soft segment and below the T_{trans} of the hard segment.

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BIODEGRADABLE SHAPE MEMORY POLYMERS

Background of the Invention

This application is generally in the area of shape memory polymers, and more particularly to biodegradable shape memory polymers.

Shape memory is the ability of a material to remember its original shape, either after mechanical deformation (Figure 1), which is a one-way effect, or by cooling and heating (Figure 2), which is a two-way effect. This phenomenon is based on a structural phase transformation.

The first materials known to have these properties were shape memory metal alloys (SMAs), including TiNi (Nitinol), CuZnAl, and FeNiAl alloys. The structure phase transformation of these materials is known as a martensitic transformation. These materials have been proposed for various uses, including vascular stents, medical guidewires, orthodontic wires, vibration dampers, pipe couplings, electrical connectors, thermostats, actuators, eyeglass frames, and brassiere underwires. These materials have not yet been widely used, in part because they are relatively expensive.

Shape memory polymers (SMPs) are being developed to replace or augment the use of SMAs, in part because the polymers are light, high in shape recovery ability, easy to manipulate, and economical as compared with SMAs. In the literature, SMPs are generally characterized as phase segregated linear block co-polymers having a hard segment and a soft segment. The hard segment is typically crystalline, with a defined melting point, and the soft segment is typically amorphous, with a defined glass transition temperature. In some embodiments, however, the hard segment is amorphous and has a glass transition temperature rather than a melting point. In other embodiments, the soft segment is crystalline and has a melting point rather than a glass transition temperature. The melting point or glass transition temperature of the soft segment is substantially less than the melting point or glass transition temperature of the hard segment.

When the SMP is heated above the melting point or glass transition temperature of the hard segment, the material can be shaped. This (original) shape can be memorized by cooling the SMP below the melting point or

glass transition temperature of the hard segment. When the shaped SMP is cooled below the melting point or glass transition temperature of the soft segment while the shape is deformed, a new (temporary) shape is fixed. The original shape is recovered by heating the material above the melting point or glass transition temperature of the soft segment but below the melting point or glass transition temperature of the hard segment. In another method for setting a temporary shape, the material is deformed at a temperature lower than the melting point or glass transition temperature of the soft segment, resulting in stress and strain being absorbed by the soft segment. When the material is heated above the melting point or glass transition temperature of the soft segment, but below the melting point (or glass transition temperature) of the hard segment, the stresses and strains are relieved and the material returns to its original shape. The recovery of the original shape, which is induced by an increase in temperature, is called the thermal shape memory effect. Properties that describe the shape memory capabilities of a material are the shape recovery of the original shape and the shape fixity of the temporary shape.

Several physical properties of SMPs other than the ability to memorize shape are significantly altered in response to external changes in temperature and stress, particularly at the melting point or glass transition temperature of the soft segment. These properties include the elastic modulus, hardness, flexibility, vapor permeability, damping, index of refraction, and dielectric constant. The elastic modulus (the ratio of the stress in a body to the corresponding strain) of an SMP can change by a factor of up to 200 when heated above the melting point or glass transition temperature of the soft segment. Also, the hardness of the material changes dramatically when the soft segment is at or above its melting point or glass transition temperature. When the material is heated to a temperature above the melting point or glass transition temperature of the soft segment, the damping ability can be up to five times higher than a conventional rubber product. The material can readily recover to its original molded shape following numerous thermal cycles, and can be heated above the melting

point of the hard segment and reshaped and cooled to fix a new original shape.

Conventional shape memory polymers generally are segmented polyurethanes and have hard segments that include aromatic moieties. U.S. Patent No. 5,145,935 to Hayashi, for example, discloses a shape memory polyurethane elastomer molded article formed from a polyurethane elastomer polymerized from of a difunctional diiiosicyanate, a difunctional polyol, and a difunctional chain extender.

Examples of polymers used to prepare hard and soft segments of known SMPs include various polyethers, polyacrylates, polyamides, polysiloxanes, polyurethanes, polyether amides, polyurethane/ureas, polyether esters, and urethane/butadiene copolymers. See, for example, U.S. Patent No. 5,506,300 to Ward et al.; U.S. Patent No. 5,145,935 to Hayashi; U.S. Patent No. 5,665,822 to Bitler et al.; and Gorden, "Applications of Shape Memory Polyurethanes," *Proceedings of the First International Conference on Shape Memory and Superelastic Technologies, SMST International Committee*, pp. 115-19 (1994).

Although these polymers have been proposed for a number of uses, their medical applications have been limited to devices which are not implanted or left in the body. It is desirable to have shape memory polymers, but which are biodegradable. Many other applications for biodegradable shape memory polymers are apparent, for example, for use in making diaper or medical drape linings, or in packagings for food or other materials where there are disposal problems. It is not apparent from the commercially available polyurethane materials that one could incorporate biodegradable materials into a shape memory polymer, and retain the structural and other phyical and chemical properties which are essential to shape memory polymers and their application. Moreover, the components of the known polyurethane shape memory polymers contain aromatic groups which would be expected to not be biocompatible.

It is therefore an object of the present invention to provide biodegradable shape memory polymers.

It is still a further object of the present invention to provide shape memory polymers with physical and chemical properties and chemical structures that are different than those in conventional shape memory polymers.

Summary of the Invention

Biodegradable shape memory polymer compositions, articles of manufacture thereof, and methods of preparation and use thereof are described. The polymer compositions include one or more hard segments and one or more soft segments, wherein the compositions are biocompatible and at least one of the segments is biodegradable or at least one of the segments is linked to another segment via a biodegradable linkage.

The melting point or glass transition temperature (hereinafter, the T_{trans}) of the hard segment is at least 10 °C, and preferably 20 °C, higher than the T_{trans} of the soft segment. The T_{trans} of the hard segment is preferably between -30 and 270 °C, and more preferably between 30 and 150 °C. The ratio by weight of the hard segment:soft segments is between about 5:95 and 95:5, preferably between 20:80 and 80:20. The shape memory polymers contain at least one physical crosslink (physical interaction of the hard segment) or contain covalent crosslinks instead of a hard segment. The shape memory polymers can also be interpenetrating networks or a semi-interpenetrating networks.

In addition to changes in state from a solid to liquid state (melting point or glass transition temperature), hard and soft segments may undergo solid to solid state transitions, and can undergo ionic interactions involving polyelectrolyte segments or supramolecular effects based on highly organized hydrogen bonds.

Any polymers that are crystalline or amorphous and that have a T_{trans} within the range defined herein can be used to form the hard and soft segments. Representative biodegradable polymers include polyhydroxy acids, polyalkanoates, polyanhydrides, polyphosphazenes, polyetheresters, polyesteramides, polyesters, and polyorthoesters. Exemplary biodegradable linkages include ester, amide, anhydride, carbonate, and orthoester linkages.

Articles of manufacture can be prepared from the shape memory polymer compositions, for example, by injection molding, blowing, extrusion, and laser ablation. To prepare an object having a shape in memory, the object can be formed at a temperature above the T_{trans} of the hard segment, and cooled to a temperature below the T_{trans} of the soft segment. If the object subsequently is formed into a second shape, the object can be returned to its original shape by heating the object above the T_{trans} of the soft segment and below the T_{trans} of the hard segment.

Thermoset polymers can be prepared by pre-shaping macromonomers, for example, by extrusion, and fix-ing the original shape at a temperature above the T_{trans} of the thermoset polymer, for example, by photocuring reactive groups on the macromonomer.

Description of the Drawings

Figure 1 is an illustration of the one-way shape memory effect.

Figure 2 is an illustration of the two-way (thermal) shape memory effect.

Figure 3 is an illustration of combinations of suitable classes of thermoplastic materials.

Figure 4 is a diagram of a reaction sequence for the synthesis of a preferred photocrosslinker.

Figure 5 is an illustration of a photoinduced shape memory effect.

Figure 6 is an illustration of the mechanism of the thermal shape memory effect for a multiblock copolymer.

Figure 7 is a graph showing stress versus elongation for a multi-block copolymer shape memory polymer.

Figure 8 is a graph showing the melting temperature of diols, dimethacrylates, and thermosets of poly(ε-caprolactone) as a function of the molar mass weight M_n of the macromonomers.

Detailed Description of the Invention

Biodegradable shape memory polymer compositions, articles of manufacture thereof, and methods of preparation and use thereof are described.

Definitions

As used herein, the term "biodegradable" refers to materials that are bioresorbable and/or degrade and/or break down by mechanical degradation upon interaction with a physiological environment into components that are metabolizable or excretable, over a period of time from minutes to three years, preferably less than one year, while maintaining the requisite structural integrity. As used herein in reference to polymers, the term "degrade" refer to cleavage of the polymer chain, such that the molecular weight stays approximately constant at the oligomer level and particles of polymer remain following degradation. The term "completely degrade" refers to cleavage of the polymer at the molecular level such that there is essentially complete mass loss. The term "degrade" as used herein includes "completely degrade" unless otherwise indicated.

A polymer is a shape memory polymer if the original shape of the polymer is recovered by heating it above a shape recovering temperature (defined as the T_{trans} of a soft segment) even if the original molded shape of the polymer is destroyed mechanically at a lower temperature than the shape recovering temperature, or if the memorized shape is recoverable by application of another stimulus.

As used herein, the term "segment" refers to a block or sequence of polymer forming part of the shape memory polymer.

As used herein, the terms hard segment and soft segment are relative terms, relating to the T_{trans} of the segments. The hard segment(s) has a higher T_{trans} than the soft segment(s).

The shape memory polymers can include at least one hard segment and at least one soft segment, or can include at least one kind of soft segment wherein at least one kind of the soft segments are crosslinked, without the presence of a hard segment.

The hard segments can be linear oligomers or polymers, and can be cyclic compounds, such as crown ethers, cyclic di-, tri-, or oligopetides, and cyclic oligo(ester amides).

The physical interaction between hard segments can be based on charge transfer complexes, hydrogen bonds, or other interactions, since some segments have melting temperatures that are higher than the degradation temperature. In these cases, there is no melting or glass transition temperature for the segment. A non-thermal mechanism, such as a solvent, is required to change the segment bonding.

The ratio by weight of the hard segment:soft segments is between about 5:95 and 95:5, preferably between 20:80 and 80:20.

Shape Memory Polymeric Compositions

Thermoplastic shape memory materials are shaped/molded to a desired shape above the T_{trans} of the hard segment(s) and cooled down to a temperature below the shape recovering temperature, where the polymer may undergo mechanical deformation and strains are generated in the polymer. The original shape of the deformed polymers are recovered by heating them to a temperature higher than their shape recovering temperature. Above this temperature, the strains in the polymer are relieved, allowing the polymer to return to its original shape. In contrast, thermoset shape memory materials are shaped/molded to a desired shape before the macromonomers used to form the thermoset polymers are polymerized. After the shape has been fixed, the macromonomers are polymerized.

The polymer compositions are preferably compressible by at least one percent or expandable by at least five one of the original thickness at a temperature below the shape recovering temperature, with the deformation being fixed by application of a stimulus such as heat, light, ultrasound, magnetic fields or electric fields. In some embodiments, the materials show a ratio of recovery of 98% (compare to experimental examples).

When significant stress is applied, resulting in an enforced mechanical deformation at a temperature lower than the shape recovering temperature, strains are retained in the soft segments or amorphous regions, and bulky shape change is kept even after the partial liberation of strain by

the elasticity of the polymer. If the configuration of the molecular chains is disturbed by influencing the regulated arrangement of molecular chains at a temperature lower than the glass transition temperature, rearrangement of the molecular chains is assumed to occur through the increase of the volume size and the decrease of the free volume content. The original shape is recovered by the contraction of the hard segment aggregates by the elevation of the temperature according to rigid control of chain conformations and the shape of the polymer is restored to the memorized shape.

In addition to changes in state from a solid to liquid state (melting point or glass transition temperature), hard or soft segments can undergo ionic interactions involving polyelectrolyte segments or supramolecular effects based on highly organized hydrogen bonds. The SM polymer can also undergo solid state to solid state transitions (e.g. change in morphology). Solid state to solid state transitions are well known to those of skill in the art, e.g. in poly(styrene-*block*-butadiene).

Various changes can take place to the structure of an object formed using the shape memory polymers. If the objects are three dimensional objects, the changes in shape can be two dimensional. If the objects are essentially two dimensional objects, such as fibers, then the changes in shape can be one dimensional, such as along the length. The thermal and electrical conductivity of the materials can also change in response to changes in temperature.

The moisture permeability of the compositions can be varied, especially when the polymer is formed into a thin film (i.e., less than about 10 μm). Some polymer compositions, in their original shape, have a sufficient permeability such that molecules of water vapor can be transmitted through the polymer film, while water molecules are not large enough to penetrate the polymer film. The resulting materials have low moisture permeability at temperatures below room temperature and high moisture permeability at temperatures above room temperature.

Stimuli other than temperature can be used to induce shape changes. As described with reference to certain embodiments below, the shape

changes can be elicited by exposure to light activation or an agent such as an ion which alters the interpolymer bonds.

I. Polymer Segments

The segments preferably are oligomers. As used herein, the term "oligomer" refers to a linear chain molecule having a molecular weight up to 15,000 Da.

The polymers are selected based on the desired glass transition temperature(s) (if at least one segment is amorphous) or the melting point(s) (if at least one segment is crystalline), which in turn is based on the desired applications, taking into consideration the environment of use. Preferably, the number average molecular weight of the polymer block is greater than 400, and is preferably in the range of between 500 and 15,000.

The transition temperature at which the polymer abruptly becomes soft and deforms can be controlled by changing the monomer composition and the kind of monomer, which enables one to adjust the shape memory effect at a desired temperature.

The thermal properties of the polymers can be detected, for example, by dynamic mechanical thermoanalysis or differential scanning calorimetry (DSC) studies. In addition the melting point can be determined using a standard melting point apparatus.

1. Thermoset or thermoplastic polymers.

The polymers can be thermoset or thermoplastic polymers, although thermoplastic polymers may be preferred due to their ease of molding.

Preferably, the degree of crystallinity of the polymer or polymeric block(s) is between 3 and 80%, more preferably between 3 and 60%. When the degree of crystallinity is greater than 80% while all soft segments are amorphous, the resulting polymer composition has poor shape memory characteristics.

The tensile modulus of the polymers below the T_{trans} is typically between 50 MPa and 2 GPa (gigapascals), whereas the tensile modulus of the polymers above the T_{trans} is typically between 1 and 500 MPa. Preferably, the ratio of elastic modulus above and below the T_{trans} is 20 or more. The

higher the ratio, the better the shape memory of the resulting polymer composition.

The polymer segments can be natural or synthetic, although synthetic polymers are preferred. The polymer segments can be biodegradable or non-biodegradable, although the resulting SMP composition is biodegradable biocompatible polymers are particularly preferred for medical applications. In general, these materials degrade by hydrolysis, by exposure to water or enzymes under physiological conditions, by surface erosion, bulk erosion, or a combination thereof. Non-biodegradable polymers used for medical applications preferably do not include aromatic groups, other than those present in naturally occurring amino acids.

Representative natural polymer segments or polymers include proteins such as zein, modified zein, casein, gelatin, gluten, serum albumin, and collagen, and polysaccharides such as alginate, celluloses, dextrans, pullulane, and polyhyaluronic acid, as well as chitin, poly(3-hydroxyalkanoate)s, especially poly(β-hydroxybutyrate), poly(3-hydroxyoctanoate) and poly(3-hydroxyfatty acids).

Representative natural biodegradable polymer segments or polymers include polysaccharides such as alginate, dextran, cellulose, collagen, and chemical derivatives thereof (substitutions, additions of chemical groups, for example, alkyl, alkylene, hydroxylations, oxidations, and other modifications routinely made by those skilled in the art), and proteins such as albumin, zein and copolymers and blends thereof, alone or in combination with synthetic polymers.

Representative synthetic polymer blocks include polyphosphazenes, poly(vinyl alcohols), polyamides, polyester amides, poly(amino acid)s, synthetic poly(amino acids), polyanhydrides, polycarbonates, polyacrylates, polyalkylenes, polyacrylamides, polyalkylene glycols, polyalkylene oxides, polyalkylene terephthalates, polyortho esters, polyvinyl ethers, polyvinyl esters, polyvinyl halides, polyvinylpyrrolidone, polyesters, polylactides, polyglycolides, polysiloxanes, polyurethanes and copolymers thereof.

Examples of suitable polyacrylates include poly(methyl methacrylate), poly(ethyl methacrylate), poly(butyl methacrylate),

poly(isobutyl methacrylate), poly(hexyl methacrylate), poly(isodecyl methacrylate), poly(lauryl methacrylate), poly(phenyl methacrylate), poly(methyl acrylate), poly(isopropyl acrylate), poly(isobutyl acrylate) and poly(octadecyl acrylate).

Synthetically modified natural polymers include cellulose derivatives such as alkyl celluloses, hydroxyalkyl celluloses, cellulose ethers, cellulose esters, nitrocelluloses, and chitosan. Examples of suitable cellulose derivatives include methyl cellulose, ethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, hydroxybutyl methyl cellulose, cellulose acetate, cellulose propionate, cellulose acetate butyrate, cellulose acetate phthalate, carboxymethyl cellulose, cellulose triacetate and cellulose sulfate sodium salt. These are collectively referred to herein as "celluloses".

Representative synthetic degradable polymer segments or polymers include polyhydroxy acids, such as polylactides, polyglycolides and copolymers thereof; poly(ethylene terephthalate); poly(hydroxybutyric acid); poly(hydroxyvaleric acid); poly[lactide-co-(ε-caprolactone)]; poly[glycolide-co-(ε-caprolactone)]; polycarbonates, poly(pseudo amino acids); poly(amino acids); poly(hydroxyalkanoate)s; polyanhydrides; polyortho esters; and blends and copolymers thereof.

Examples of non-biodegradable polymer segments or polymers include ethylene vinyl acetate, poly(meth)acrylic acid, polyamides, polyethylene, polypropylene, polystyrene, polyvinyl chloride, polyvinylphenol, and copolymers and mixtures thereof.

Rapidly bioerodible polymers such as poly(lactide-co-glycolide)s, polyanhydrides, and polyorthoesters, which have carboxylic groups exposed on the external surface as the smooth surface of the polymer erodes, also can be used. In addition, polymers containing labile bonds, such as polyanhydrides and polyesters, are well known for their hydrolytic reactivity. Their hydrolytic degradation rates can generally be altered by simple changes in the polymer backbone and their sequence structure.

Various polymers, such as polyacetylene and polypyrrole, are conducting polymers. These materials are particularly preferred for uses in which electrical conductance is important. Examples of these uses include

tissue engineering and any biomedical application where cell growth is to be stimulated. These materials may find particular utility in the field of computer science, as they are able to absorb heat without increasing in temperature better than SMAs. Conducting shape memory polymers are useful in the field of tissue engineering to stimulate the growth of tissue, for example, nerve tissue.

2. Hydrogels.

The polymer may be in the form of a hydrogel (typically absorbing up to about 90% by weight of water), and can optionally be ionically crosslinked with multivalent ions or polymers. Ionic crosslinking between soft segments can be used to hold a structure, which, when deformed, can be reformed by breaking the ionic crosslinks between the soft segments. The polymer may also be in the form of a gel in solvents other than water or aqueous solutions. In these polymers, the temporary shape can be fixed by hydrophilic interactions between soft segments.

Hydrogels can be formed from polyethylene glycol, polyethylene oxide, polyvinyl alcohol, polyvinyl pyrrolidone, polyacrylates, poly (ethylene terephthalate), poly(vinyl acetate), and copolymers and blends thereof. Several polymeric segments, for example, acrylic acid, are elastomeric only when the polymer is hydrated and hydrogels are formed. Other polymeric segments, for example, methacrylic acid, are crystalline and capable of melting even when the polymers are not hydrated. Either type of polymeric block can be used, depending on the desired application and conditions of use.

For example, shape memory is observed for acrylic acid copolymers only in the hydrogel state, because the acrylic acid units are substantially hydrated and behave like a soft elastomer with a very low glass transition temperature. The dry polymers are not shape memory polymers. When dry, the acrylic acid units behave as a hard plastic even above the glass transition temperature and show no abrupt change in mechanical properties on heating. In contrast, copolymers including methyl acrylate polymeric segments as the soft segments show shape memory properties even when dry.

3. Polymers Capable of Forming a Gel at Increased Temperatures.

Certain polymers, for example, poly(ethylene oxide-co-propylene oxide) (PLURONICS™), are soluble in water at temperatures lower than body temperature and become hydrogels at temperatures higher than body temperature. Incorporation of these polymers as segments in shape memory polymers provides them with the ability to response to changes in temperature in a manner opposite that of typical shape memory polymers. These materials recover their shape when cooled below their shape recovery temperature, rather than being heated above their shape recovery temperature. This effect is called inversed thermal shape memory effect. Shape memory polymer compositions including these polymer segments are useful in various biomedical applications where the polymer can be inserted as a liquid, and cooled to recover an intended shape *in situ*. The inverse thermal shape memory effect can be obtained by incorporating two different segments into a polymer that are miscible at temperatures lower than T_{misc}, but are immiscible at higher temperatures. The phase separation at higher temperatures stabilizes the temporary shape.

The polymers can be obtained from commercial sources such as Sigma Chemical Co., St. Louis, MO.; Polysciences, Warrenton, PA; Aldrich Chemical Co., Milwaukee, WI; Fluka, Ronkonkoma, NY; and BioRad, Richmond, CA. Alternately, the polymers can be synthesized from monomers obtained from commercial sources, using standard techniques.

II. Assembly of Polymer Segments

The shape memory polymer include one or more hard segments and one or more soft segments, wherein at least one of the segments is biodegradable or at least one of the segments is linked to another segment via a biodegradable linkage. Representative biodegradable linkages include ester-, amide-, anhydride-, carbonate-, or orthoester linkages.

1. Polymer Structures.

The shape memory effect is based on the polymer morphology. With respect to thermoplastic elastomers, the original shape of an object is fixed by physical crosslinks caused by the hard segment. With respect to

thermoset polymers, the soft segments are covalently crosslinked instead of having hard segments. The original shape is set by the crosslinking process.

In contrast to prior art segmented polyurethane SMPs, the segments of the compositions described herein need not be linear. The segments can be partially grafted or attached in dendremeric side groups.

A. Thermoplastic and Thermoelastic Polymers

The polymers can be in the form of linear diblock-, triblock-, tetrablock, or multiblock copolymers, branch or graft polymers, thermoplastic elastomers, which contain dendritic structures, and blends thereof. Figure 3 illustrates some of the combinations of suitable classes of thermoplastic materials forming the hard and soft segments. The thermoplastic shape memory polymer composition also can be a blend of one or more homo- or co-polymer with one or more diblock-, triblock-, tetrablock, or multiblock copolymers, branch or graft polymers. These types of polymers are well known to those of skill in the art.

As used herein, the term "degradable thermoset" refers to (i) thermosets SMPs containing only one soft segment, which contains cleavable bonds, and (ii) thermosets containing more than one soft segment, wherein at least one soft segment is degradable or wherein the different soft segments are connected by cleavable bonds. There are four different types of thermoset polymers that have shape memory capability. These include polymer networks, semi-interpenetrating networks, interpenetrating networks, and mixed-interpenetrating networks.

i. Polymer Networks

A polymer network is prepared by covalently crosslinking macromonomers, i.e., polymers which contain polymerizable endgroups such as carbon-carbon double bonds. The polymerization process can be induced by using light or heat sensitive initiators or by curing with ultraviolet light ("UV-light") without an initiator. Shape memory polymer networks are prepared by crosslinking one or more soft segments which correspond to one or more thermal transitions.

In an embodiment preferred for biomedical applications, the crosslinking is performed using a photocrosslinker and requires no chemical

initiator. The photocrosslinker advantageously eliminates the need for initiator molecules, which may be toxic. Figure 4 is a diagram of a reaction sequence for the synthesis of a preferred photocrosslinker, which produces an overall yield of about 65%.

ii. Interpenetrating Networks

Interpenetrating networks ("IPN") are defined as networks where two components are crosslinked, but not to each other. The original shape is determined by the network with the highest crosslink density and the highest mechanical strength. The material has at least two T_{trans} corresponding to the different soft segments of both networks.

iii. Mixed Interpenetrating Network

A mixed IPN includes at least one physically crosslinked polymer network (a thermoplastic polymer) and at least one covalently crosslinked polymer network (a thermoset polymer) that cannot be separated by any physical methods. The original shape is set by the covalently crosslinked network. The temporary shapes correspond to the T_{trans} of the soft segments and the T_{trans} of the hard segment of the thermoplastic elastomer component.

A particularly preferred mixed interpenetrating network is prepared by polymerizing a reactive macromonomer in the presence of a thermoplastic polymer, for example, by the photopolymerization of carbon-carbon double bonds. In this embodiment, the ratio by weight of thermoset polymer to thermoplastic polymer is preferably between 5:95 and 95:5, more preferably, between 20:80 and 80:20.

iv. Semi-Interpenetrating Networks

Semi-interpenetrating networks ("semi-IPN") are defined as two independent components, where one component is a crosslinked polymer (a polymer network) and the other component is a non-crosslinked polymer (a homopolymer or copolymer), wherein the components cannot be separated by physical methods. The semi-IPN has at least one thermal transition corresponding to the soft segment(s) and the homo- or co-polymer components. The crosslinked polymer preferably constitutes between about 10 and 90% by weight of the semi-interpenetrating network composition.

v. Polymer Blends

In a preferred embodiment, the shape memory polymer compositions described herein are formed of a biodegradable polymer blend. As used herein, a "biodegradable polymer blend" is a blend having at least one biodegradable polymer.

The shape memory polymers can exist as physical mixtures of thermoplastic polymers. In one embodiment, a shape memory polymer composition can be prepared by interacting or blending two thermoplastic polymers. The polymers can be semicrystalline homopolymers, semicrystalline copolymers, thermoplastic elastomers with linear chains, thermoplastic elastomers with side chains or any kind of dendritic structural elements, and branched copolymers, and these can be blended in any combination thereof.

For example, a multiblock copolymer with a hard segment with a relatively high T_{trans} and a soft segment with a relatively low T_{trans} can be mixed or blended with a second multiblock copolymer with a hard segment with a relatively low T_{trans} and the same soft segment as that in the first multiblock copolymer. The soft segments in both multiblock copolymers are identical, so the polymers are miscible in each other when the soft segments are melted. There are three transition temperatures in the resulting blend - that of the first hard segment, that of the second hard segment, and that of the soft segment. Accordingly, these materials are able to memorize two different shapes. The mechanical properties of these polymers can be adjusted by the changing the weight ratio of the two polymers.

Other kinds of blends of at least two multiblock copolymers, in which at least one of the segments is miscible with at least one of the segments of the other multiblock copolymers, can be prepared. If two different segments are miscible and build one domain together, then the thermal transition of this domain depends on the weight content of the two segments. The maximum number of memorized shapes results from the number of thermal transitions of the blend.

Shape memory blends may have better shape memory capabilities than the blend components alone. Shape memory blends are composed of at

least one multiblock copolymer and at least one homo- or copolymer. In principle di-, tri, tetra-block copolymers can be used instead of a multiblock copolymer.

Shape memory blends are highly useful in industrial applications, since a broad range of mechanical, thermal, and shape memory capabilities can be obtained from only two or three basic polymers by blending them in different weight ratios. A twin screw extruder is an example of standard process equipment that could be used to mix the components and process the blend.

III. Methods of Making the SMPs

The polymers described above are either commercially available or can be synthesized using routine chemistry. Those of skill in the art can readily prepare the polymers using known chemistry. Examples 1 and 2 below describe experimental procedures used to prepare the SMPs.

IV. Methods of Shaping the SMP Compositions

The compositions can be formed into a first shape under appropriate conditions, for example, at a temperature above the T_{trans} of the hard segments, and allowed to cool below the T_{trans} of the soft segment(s). Standard techniques are extrusion and injection molding. Optionally, the object can be re-formed into a second shape. Upon application of heat or other appropriate set of conditions, the object returns to original shape.

Thermoset polymers can be prepared by extruding the pre-polymerized material (macromonomers), and fixing the original shape at a temperature above the T_{trans} of the thermoset polymer, for example, by photocuring reactive groups on the monomer. The temporary shape is fixed by cooling the material below T_{trans} after deforming the material. Figure 5 illustrates a photoinduced shape memory effect.

The crosslinking also can be performed in a solution of the macromonomers. The solvent is removed from the formed gel in a subsequent step.

Those compositions formed of thermoplastic polymers can be blown, extruded into sheets or shaped by injection molding, for example, to form fibers. The compositions can also be shaped by other methods known to

those of skill in the art for shaping solid objects, for example, laser ablation, micromachining, use of a hot wire, and by CAD/CAM (computer aided design/computer aided manufacture) processes. These processes are preferred for shaping thermoset polymers.

V. Therapeutic, Prophylactic, and Diagnostic Applications

Any of a variety of therapeutic, prophylactic and/or diagnostic agents can be incorporated within the polymer compositions, which can locally or systemically deliver the incorporated agents following administration to a patient.

1. Therapeutic, Diagnostic and Prophylactic Applications

Any of a variety of therapeutic agents can be incorporated within the particles, for local or systemic delivery of the incorporated agents following administration to a patient. Examples include synthetic inorganic and organic compounds or molecules, proteins and peptides, polysaccharides and other sugars, lipids, and nucleic acid molecules having therapeutic, prophylactic or diagnostic activities. Nucleic acid molecules include genes, plasmid DNA, naked DNA, antisense molecules which bind to complementary DNA to inhibit transcription, ribozymes and ribozyme guide sequences. The agents to be incorporated can have a variety of biological activities, such as vasoactive agents, neuroactive agents, hormones, growth factors, cytokines, anaesthetics, steroids, anticoagulants, anti-inflammatories, immunomodulating agents, cytotoxic agents, prophylactic agents, antibiotics, antivirals, antisense, antigens, and antibodies. In some instances, the proteins may be antibodies or antigens which otherwise would have to be administered by injection to elicit an appropriate response. Proteins are defined as consisting of 100 amino acid residues or more; peptides are less than 100 amino acid residues. Unless otherwise stated, the term protein refers to both proteins and peptides. Polysaccharides, such as heparin, can also be administered. Compounds with a wide range of molecular weight, for example, between 10 and 500,000 grams per mole, can be encapsulated.

Imaging agents which may be utilized include commercially available agents used in positron emission tomography (PET), computer assisted tomography (CAT), single photon emission computerized

tomography, x-ray, fluoroscopy, magnetic resonance imaging (MRI), and ultrasound agents.

VI. Articles, Devices and Coatings

The SMP compositions can be used to prepare numerous articles of manufacture, for use in biomedical and other applications.

1. Articles and Devices for Biomedical Applications

The polymer compositions can be used to prepare articles of manufacture for use in biomedical applications. For example, sutures, orthodontic materials, bone screws, nails, plates, catheters, tubes, films, stents, orthopedic braces, splints, tape for preparing casts, and scaffolds for tissue engineering, contact lenses, drug delivery devices, implants, and thermal indicators, can be prepared.

The SMP compositions are preferably prepared from biocompatible polymers, and, for most applications, from biodegradable polymers. Biodegradable polymers degrade at a controlled rate depending on the composition and crosslinking of the polymer. Degradable polymeric implants eliminate the need for implant retrieval and can be used simultaneously to deliver therapeutic agents.

The materials can be used in many applications requiring load-bearing capacities and controlled degradation.

The polymer compositions can be formed into the shape of an implant which can be implanted within the body to serve a mechanical function. Examples of such implants include rods, pins, screws, plates and anatomical shapes.

A particularly preferred use of the compositions is to prepare sutures that have a rigid enough composition to provide for ease of insertion, but upon attaining body temperature, soften and form a second shape that is more comfortable for the patient while still allowing healing.

Another preferred use is in the area of catheters. A catheter can be rigid at body temperature for ease of insertion, but, after warming to body temperature, can soften to provide comfort to the patient.

The polymer compositions can be combined with fillers, reinforcement materials, radioimaging materials, excipients or other

materials as needed for a particular implant application. Examples of fillers include calcium-sodium-metaphosphate which is described in U.S. Patent No. 5,108,755. Those of skill in the art can readily determine a suitable amount of these materials to include in the compositions.

The articles can incorporate various therapeutic and/or diagnostic agents, as described above.

2. Non-Medical Applications

There are numerous applications for the shape memory polymer compositions other than biomedical applications.

Examples of non-medical type applications for biodegradable polymers include items for which disposal is an issue, such as disposable diapers and packaging materials.

3. Coatings with controlled degradation

Shape memory polymers can be designed so that the degradation rate is varied. For example, in one embodiment, a hydrolytically degradable polymer can be selectively protected by applying a hydrophobic SMP coating that temporarily prevents water from reaching the hydrolytically cleavable bonds of the bulk polymer. The protective feature of the coating then can be modified when desired by applying an external stimulus such that the diffusion properties of coating are altered to permit water or other aqueous solutions to permeate through the coating and initiate the degradation process. If the hydrolysis rate is relatively high compared to the diffusion rate of water, then the diffusion rate of water through the coating determines the degradation rate. In another embodiment, a hydrophobic coating consisting of densely crosslinked soft segments can be used as a diffusion barrier for water or aqueous solutions. The soft segments should be at least partially crosslinked by linkages that can be cleaved by application of a stimulus. The diffusion rate of water can increased by lowering the crosslinking density.

VII. Methods of Use

Certain articles of manufacture are designed to hold their intended shape unless acted upon in a manner inconsistent with their normal use. For example, a car bumper will hold its intended shape unless it has been

impacted. These articles of manufacture are to be used in their intended shape and repaired, for example, by application of heat, once they are damaged.

Other articles of manufacture are designed to be used such that the first shape is intended for an initial use, and a second shape is intended for a subsequent use. Examples of these include biomedical devices which can form a second shape upon reaching at body temperature, or upon application of an external stimulus which heats the device above body temperature.

Still other articles of manufacture are designed to be used such that their shape changes in reaction to, or adjustment to, changes in temperature, such as thermosensers in medical devices.

The present invention will be further understood with reference to the following non-limiting examples.

Example 1: Copolyesterurethane Shape Memory Polymers

A group of biocompatible and biodegradable multiblock-copolymers showing a thermal shape memory effect was synthesized. These polymers were composed of a crystallizable hard segment (T_m) and a soft segment having a thermal transition temperature T_{trans} between room and body temperature. In contrast to the prior art segmented polyurethanes, the hard segment was an oligoester or an oligoetherester and did not contain any aromatic component.

The mechanism for programming the temporary shape and recovering the permanent shape of a multiblock-copolymer is shown in Figure 6. The permanent shape of the materials was set by melting the polymer and cooling above T_{trans} (Fig. 6 – top pos.). Then, the polymer was formed into its temporary shape (Fig. 6 – right pos.), which was fixed by cooling below T_{trans} (Fig. 6 – bottom pos.). After unloading, the permanent shape was recovered by reheating above T_{trans}.

Synthesis of Telechelics, oligomers with functional groups at both ends.

The telechelic macrodiol were synthesized by ring opening polymerization of cyclic monomers with di(n-butyl)tinoxide as a transesterfication catalyst under a N_2 atmosphere.

Hard Segment

α,ω-dihydroxy [oligo(ethylene glycol glycolate) ethylene oligo (ethylene glycol glycolate)] - (PDS1200 and PDS1300) was prepared as follows. The monomer p-dioxane-2-one was obtained by distillation (thermal depolymerization) of the oligomer prior to use. 57 g (0.63 mol) of the monomer, 0.673 g (10.9 mmol) ethylene glycol, and 0.192 g (0.773 mmol) di(n-butyl) tinoxide were heated to 80 °C for 24 h. The end of the reaction (equilibrium) was determined by GPC. The product was soluted in hot 1,2-dichloroethane and filtered hot through a Buechner-funnel filled with silica gel. The product was obtained by precipitation in hexanes and dried in vacuo for 6 h.

Soft Segment

i. Crystalline

Poly(ε-caprolactone)-diols with different M_n are commercially available, for example, from Aldrich and Polysciences. PCL-2000 was used herein.

ii. Amorphous

α,ω-dihydroxy [oligo(*L*-lactate-*co*-glycolate) ethylene oligo (*L*-lactate-*co*-glycolate)] - (abbr.: PLGA2000-15) was prepared as follows. In a 1000 ml two-neck round bottomed flask, 300 g (2.08 mol) of L,L-dilactide, 45 g (0.34 mol) of diglycolide and 4.94 g (0.80 mol) ethylene glycol were heated to melt at 40 °C and stirred. 0.614 g (2.5 mmol) di(n-butyl) tinoxide was added. After 7 h, the reaction reached equilibrium as determined by GPC. The reaction mixture was soluted in 1,2-dichloroethane and purified in a silica gel column. The product was obtained by precipitation in hexanes and dried *in vacuo* for 6 h.

Properties of Telechelics

The molecular weight M_n and thermal properties of the macrodiols were determined as shown in Table 1 below.

Table 1: Molecular Weight and Thermal Properties of the Macrodiols

Label	M_n GPC [$g \cdot mol^{-1}$]	M_n VPO [$g \cdot mol^{-1}$]	T_m [°C]	ΔH [$J \cdot g^{-1}$]	T_g [°C]	ΔC_p [$J \cdot g^{-1}$]
PCL2000	1980	1690	43	73.5	<-40	-
PDS1300	1540	1340	97	74.5	<-20	-
PDS1200	2880	1230	95	75.0	<-20	-

PLGA2000	2020	1960	-	-	29.0	0.62

Synthesis of Thermoplastic Elastomers (Multiblock Copolymer)

In a 100 ml two-neck round-bottomed flask connected to a soxleth extractor filled with molecular sieve 0.4 nm, two different macrodiols (one hard segment and one soft segment) as described in Table 2 below were soluted in 80 ml 1,2-dichloroethane. The mixture was refluxed to dry by azeotropic extraction of the solvent. Freshly distilled trimethylhexane-1,6-diisocyanate was added with a syringe, and the reaction mixture was heated to 80 °C for at least 10 days. At regular intervals, samples of the mixture were taken to determine the molecular weight of the polymer by GPC. At the end of the reaction, the product was obtained by precipitating the polymer in hexanes and purified by repeatedly dissolving in 1,2-dichloroethane and precipiting in hexanes.

Multiblock copolymers were prepared from the following two types of polymers.

(i) PDC polymers contain poly(ε-caprolactone). T_{trans} for the soft segment is the melting point.

(ii) PDL polymers contain a α,ω-dihydroxy [oligo(*L*-lactate-*co*-glycolate) ethylene oligo (*L*-lactate-*co*-glycolate)]. T_{trans} for the soft segment is the glass transition point.

Table 2: Synthesis of Multiblock Copolymers

Polymer	1. Diol	m [g]	n [mmol]	2. Diol	m [g]	n [mmol]	TMDI [mmol]	time [d]
PDC*22*	PDS1200	3,0245	2,653	PCL2k	6,0485	3,024	5,738	10
PDL*23*	PDS1200	2,2787	2,000	PLGA2k	6.1443	3,070	5,163	10
PDC*27*	PDS1300	2,5859	1,724	PCL2k	5,3611	2,681	4,368	14
PDC*40*	PDS1300	3,6502	2,433	PCL2k	3,9147	1,957	4,510	13
PDC*31*	PDS1300	3,2906	2,194	PCL2k	4,8619	2,431	4,500	16
PDL*30*	PDS1300	3,7115	2,474	PLGA2k	4,0205	2,011	4,480	16

Properties of the Thermoplastic Elastomers

The physical, mechanical, and degradation properties determined for the compositions are provided in Tables 3-9 below.

The hydrolytic degradation behavior of the new materials were tested in buffer solution pH 7 at 37 °C. It was shown that the polymers are

completely degradable and their degradation rate can be adjusted by the concentration of easily hydrolysable ester bonds. The values for loss of relative mass $m_r = m(t_0)/m(t)$ in % at 37 °C, and. loss of relative molecular weight $M_r = M_w(t)/M_w(t_0)$ in % at 37°C:

The toxicity of two different multiblock-copolymers was investigated using a chicken egg test. It was shown that blood vessels developed regularly and their condition was not influenced by the polymer samples.

Table 3: Composition of the Copolyester Urethanes Determined by 400 MHz ^{1}H-NMR-Spectroscopy

Label	Hard Segment	Weight Content [%]*	Soft Segment	Weight Content [%]*
PDL*23*	PDS	23.0	PLGA	54.2
PDL*30*	PDS	30.0	PLGA	52.1
PDC*22*	PDS	22.0	PCL	64.5
PDC*27*	PDS	27.0	PCL	61.1
PDC*31*	PDS	31.1	PCL	55.4
PDC*40*	PDS	40.4	PCL	46.2

* The difference to 100% is the urethane content.

Table 4: Molecular Weight M_w of the Copolyester Urethanes Films Determined by Multidetector-GPC

Label	Polymer Film		
	M_w(LS) [g·mol^{-1}]	M_w(Visc) [g·mol^{-1}]	dn/dc [ml·g^{-1}]
PDL*23*	161,500	149,000	0.065
PDL*30*	79,100	83,600	0.057
PDC*22*	119,900	78,500	0.078
PDC*27*	72,700	61,100	0.080
PDC*31*	110,600	108,600	0.065
PDC*40*	93.200	86.300	0.084

Table 5: Transition Temperatures T_m and T_g, Enthalpies of Fusion ΔH_m and Change in Heat Capacity Δc_p of the Polymer Films from DSC Measurements (Values Given from Second Heating Process)

Label	T_{m1} [°C]	ΔH_{m1} [J·g^{-1}]	T_g [°C]	ΔC_p [J·g^{-1}]	T_{m2} [°C]	ΔH_{m2} [J·g^{-1}]
PDL23	-	-	34.5	0.38	-	-
PDL30	-	-	33.5	0.25	85.0	8.5
PDC22	35.0	26.0	-	-	-	-
PDC27	37.0	25.0	-	-	75,5	3.5
PDC31	36.5	28.5	-	-	76,5	5.5
PDC40	35.0	7.0	-	-	77,5	7.0

Table 6: Mechanical Properties of Polymer Films at 50 °C from Tensile Tests

Code	E-Modulus [MPa]	ε_r [%]	σ_r [MPa]	ε_{max} [%]	σ_{max} [MPa]
PDC*27*	1.5	1,350	2.1	1,300	2.3
PDC*31*	1.5	1,400	4.9	1,300.	5.4
PDC*40*	4.0	1,250	5.8	1,300	5.9
PDL*30*	2.0	1,400	2.1	1,250	2.3

Table 7: PDL22 Degradability

Degradation Time [d]	M_r(viscosimetry) [%]	M_r(light scattering) [%]
14	81.3	85.7
21	67.1	74.6
29	62.9	65.6
42	43.6	47.7
56	54.4	41.9

Table 8: PDL23 Degradability

Degradation Time [d]	M_r(viscosimetry) [%]	M_r(light scattering) [%]
14	61.1	87.3
21	40.7	76.7
29	32.8	62.2
42	17.4	46.7
56	16.9	18.5

Table 9: Loss of Relative Mass

	PDC*22*	PDL*23*
Degradation Time [%]	m_r [%]	m_r [%]
14	99.2	98.1
21	99.3	97.5
29	98.6	97.2
42	98.3	96.9
56	97.3	93.3

Shape Memory Properties

Figure 7 shows the results of tensile tests performed on the multiblock copolymers, as a function of the number of thermolytic cycles. The average shape fixity rate of thermocyclicly treated polymers and the dependency of strain recovery rates as a function of the number of cycles is

shown below in Tables 10 and 11, respectively. The polymers have a high shape fixity, and an equilibrium state was achieved after only two cycles.

Table 10: Average Shape Fixity Rate R_f

Label	R_f [%]
PDC*27*	97.9
PDC*40*	96.2
PDL*30*	97.7

Table 11: Cycle Number Dependence of Strain Recovery Rates R_r

	PDC*27*	PDC*40*	PDL*23*
Number of Cycles	R_r [%]	R_r [%]	R_r [%]
2	77.3	73.7	93.8
3	93.2	96.3	98.8
4	98.5	98.7	98.9
5	98.5	98.7	98.8

Example 2: Degradable Shape Memory Thermoset With Crystallizable Soft Segment

A range of poly(ε-caprolactone) dimethacrylates and thermosets were evaluated for their mechanical and shape memory properties.

Synthesis of Macromonomer

Poly(ε-caprolactone) dimethacrylates (PCLDMAs) were prepared as follows. To a solution of poly(ε-caprolactone) diol with M_n = 2'000 $gmol^{-1}$ (20.0 g, 10 mmol) and triethylamine (5.3 mL, 38 mmol) in 200 mL of dry THF, methacryloyl chloride (3.7 mL, 38 mmol) was added dropwise at 0 °C. The solution was stirred at 0 °C for 3 days and precipitated salt filtered off. After concentrating the mixture at room temperature under reduced pressure, 200 mL of ethyl acetate was added, and the solution filtered again and precipitated into a ten-fold excess of a mixture of hexanes, ethyl ether, and methanol (18:1:1). The colorless precipitate was collected, soluted in 200 mL of dichloroethane, precipitated again, and dried carefully at room temperature at reduced pressure.

Synthesis of Thermosets

The macromonomer (or the monomer mixture) was heated to 10 °C above its melting temperature (T_m) and filled into a mould formed by two

glass plates (25 mm x 75 mm) and a teflon spacer of 0.60 mm thickness. To achieve a good homogenity, the mould was stored at T_m for another hour. Photocuring was performed on a heated plate at T_m for 15 min. The distance between heat lamp head and sample was 5.0 cm. After cooling to room temperature, the sample was extracted and swollen with a 100-fold excess of dichloromethane overnight and washed carefully. Finally, the sample was dried at room temperature under reduced pressure.

Properties of Macromonomers and Thermosets

Table 12 below lists the poly(ε-caprolactone) dimethacrylates that were prepared, along with the respective degree of acrylation (D_a) (%) The number following PCLDMA is the molecular weight M_n of the poly(ε-caprolactone) diol used in the synthesis as determined using ^{1}H-NMR and GPC, rounded to 500.

Table 12: Poly(ε-caprolactone) Diol and Degree of Acrylation

Name	D_a [%]
PCLDMA1500	87
PCLDMA2000	92
PCLDMA3500	96
PCLDMA4500	87
PCLDMA6500	93
PCLDMA7000	85
PCLDMA10000	86

Figure 8 shows the melting temperature (T_m) of diols, dimethacrylates, and thermosets of poly(ε-caprolactone) as a function of the molar mass weight M_n of the macromonomers. In the graph, macrodiols are represented by - -■- - ; macromoners by ···●···; and thermosets by —▲—.

The tensile properties of poly(ε-caprolactone) thermosets C1 through C7 at room temperature are shown below in Table 13, wherein E is the elastic modulus (Young's modulus), ε_S is the elongation and σ_S is the stress at the yield point, σ_{max} is the maximum stress, ε_{max} is the elongation at σ_{max}, ε_R is the elongation at break, and σ_R is the stress at break. Table 14 provided below shows the tensile properties of the same poly(ε-caprolactone) thermosets at 70 °C.

Table 13: Thermoset Tensile Properties at Room Temperature

name	E [MPa]	ε_S [%]	σ_S [MPa]	ε_{max} [%]	σ_{max} [MPa]	ε_R [%]	σ_R [MPa]
C1	2.4±0.6	-	-	16.1±2.0	0.4±0.1	16.1±2.3	0.38±0.02
C2	35±3	-	-	20.6±0.3	4.7±0.1	20.6±0.3	4.7±0.1
C3	38±1	48±1	11.2±0.1	180±20	12.1±1.2	190±20	11.7±1.6
C4	58±4	54±1	12.2±0.1	247±4	13.6±1.9	248±13	15.5±2.7
C5	72±1	56±2	15.5±0.2	275±10	15.6±1.7	276±6	15.0±1.0
C6	71±3	43±2	14.2±0.1	296±14	15.5±0.2	305±8	13.8±2.7
C7	71±2	42±5	13.6±0.2	290±30	16.2±0.5	290±30	15.7±0.9

Table 14: Thermoset Tensile Properties at 70 °C

name	E [MPa]	σ_{max} [MPa]	ε_R [%]
C1	1.84 ± 0.03	0.40 ± 0.08	24 ± 6
C2	2.20 ± 0.12	0.38 ± 0.05	18 ± 2
C3	6.01 ± 0.12	2.05 ± 0.21	43 ± 9
C4	2.30 ± 0.16	0.96 ± 0.01	61 ± 3
C5	1.25 ± 0.08	0.97 ± 0.15	114 ± 13
C6	1.91 ± 0.11	1.18 ± 0.06	105 ± 11
C7	0.70 ± 0.09	0.79 ± 0.10	210 ± 7

Shape Memory Properties

The thermosets were determined to have the thermomechanical properties indicated in Table 15. The number average molecular weights (M_n) is of the macromonomer. The lower limit temperature, T_l, is 0 °C, and the higher limit temperature, T_h, is 70 °C. The extension in the temporary shape is 50%. $R_r(2)$ is the strain recovery rate of the second cycle, $R_{r,tot}$ is the total strain recovery rate after 5 cycles, R_f is the average strain fixity rate.

Table 15: Thermoset Thermomechanical Properties

name	M_n [$g \cdot mol^{-1}$]	$R_r(2)$ [%]	$R_{r,tot}$ [%]	R_f [%]
C4	4,500	93.3	93.0	93.9± 0.2
C5	6,500	96.3	94.5	93.9± 0.2
C6	7,000	93.8	92.1	92.5± 0.1
C7	10,000	98.6	96.8	86.3± 0.5

We claim:

1. A biodegradable shape memory polymer composition.

2. The composition of claim 1 comprising:

a) at least one hard segment which has a T_{trans} between -40 and 270 °C,

b) at least one soft segment which has a T_{trans} at least 10 °C lower than that of the hard segment(s), which is linked to at least one hard segment,

wherein at least one of the hard or soft segments includes a biodegradable region or at least one of the hard segment(s) is linked to at least one of the soft segment(s) through a biodegradable linkage.

3. The composition of claim 2 wherein the T_{trans} of the hard segment is in the range of between 30 and 150 °C.

4. The composition of claim 3 wherein the T_{trans} of the hard segment is in the range of between 30 and 100 °C.

5. The composition of claim 2 wherein the T_{trans} of the soft segment(s) is at least 20 °C below that of the hard segment(s).

6. The composition of claim 2 wherein at least one of the hard and soft segments is a thermoplastic polymer.

7. The composition of claim 2 wherein the hard segment comprises cyclic moieties.

8. The composition of claim 2 wherein the ratio by weight of the hard and soft segments is between about 5:95 and 95:5.

9. The composition of claim 1 wherein the shape memory polymer is selected from the group consisting of graft polymers, linear polymers, and dendrimer polymers.

10. The composition of claim 1 wherein polymer comprises a biodegradable region selected from the group consisting of polyhydroxy acids, poly(ether ester)s, polyorthoesters, poly(amino acids), synthetic poly(amino acids), polyanhydrides, polycarbonates, poly(hydroxyalkanoate)s, and poly(ε-caprolactone)s.

11. The composition of claim 1 wherein the polymer comprises a biodegradable linkage selected from the group consisting of ester groups, carbonate groups, amide groups, anhydride groups, and orthoester groups.

12. The composition of claim 1 wherein the polymer is completely degradable.

13. The composition of claim 1 comprising:

a degradable thermoset polymer that comprises a covalently crosslinked crystallizable soft segment having a T_m between 250 °C and –40 °C.

14. The composition of claim 13 wherein the degradable thermoset polymer comprises a covalently crosslinked crystallizable soft segment having a T_m between 200 °C and 0 °C.

15. The composition of claim 1 comprising

a) at least one first segment which has a T_{trans} between -40 and 270 °C,

b) at least one second segment which is linked to at least one first segment, and which comprises ionic interactions of sufficient strength that the second segment has no melting or glass transition temperature,

wherein at least one of the first or second segments includes a biodegradable region or at least one of the first segments is linked to at least one of the second segments through a biodegradable linkage.

16. The composition of claim 15 wherein the ionic interaction comprises polyelectrolyte segments or supramolecular effects based on highly organized hydrogen bonds.

17. The composition of claim 1 wherein the polymer has an inverse temperature effect.

18. The composition of claim 1 wherein the polymer changes shape in response to light.

19. The composition of claim 1 wherein the polymer is a polymer blend.

20. The composition of claim 1 comprising a coating altering the degradation of the shape memory polymer.

21. An article comprising the biodegradable shape memory polymer composition of any of claims 1-20.

22. The article of claim 21 incorporating an agent selected from the group consisting of therapeutic, diagnostic and prophylactic agents.

23. The article of claim 21 wherein the article is implantable and the biodegradable shape memory polymer is biocompatible.

24. The article of claim 23 wherein the shape memory polymer does not contain aromatic groups.

25. The article of claim 21 wherein the article is a medical device selected from the group consisting of stents, catheters, prosthetics, grafts, screws, pins, pumps, and meshes.

FIG. 1

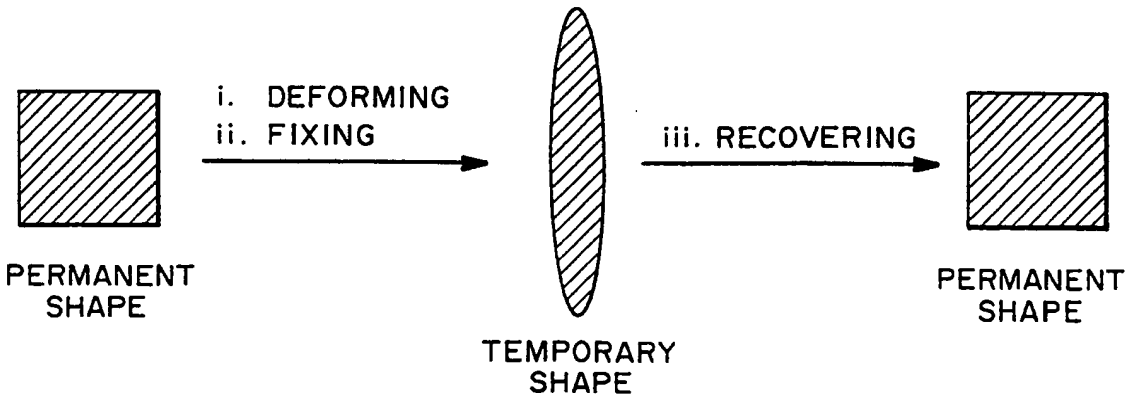
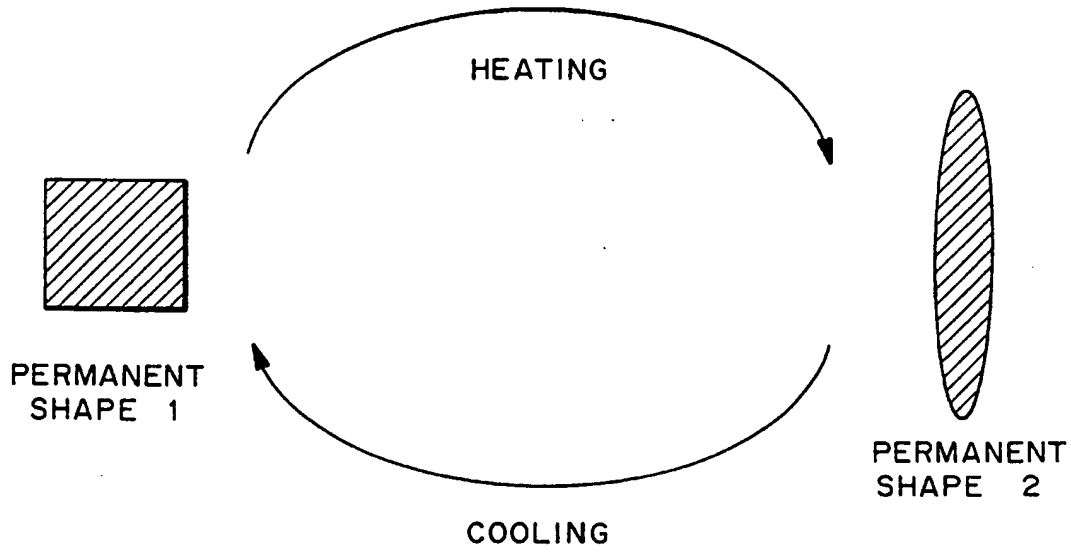

i. DEFORMING
ii. FIXING
iii. RECOVERING
PERMANENT SHAPE
TEMPORARY SHAPE
PERMANENT SHAPE

FIG. 2


HEATING
PERMANENT SHAPE 1
PERMANENT SHAPE 2
COOLING

P=THERMOPLASTIC MATERIALS

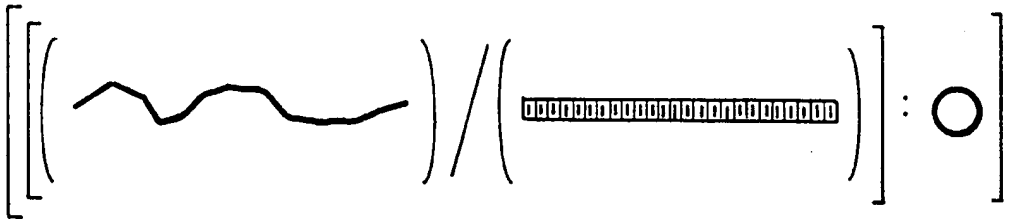
SOFT SEGMENT

HARD SEGMENT

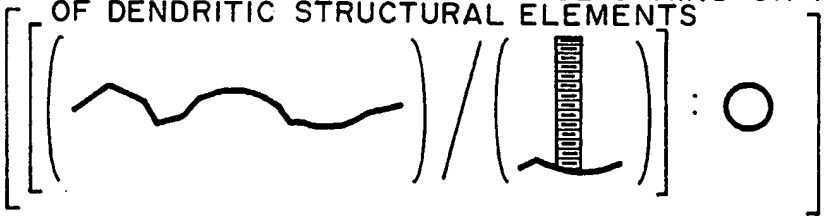
O-JUNCTION UNIT

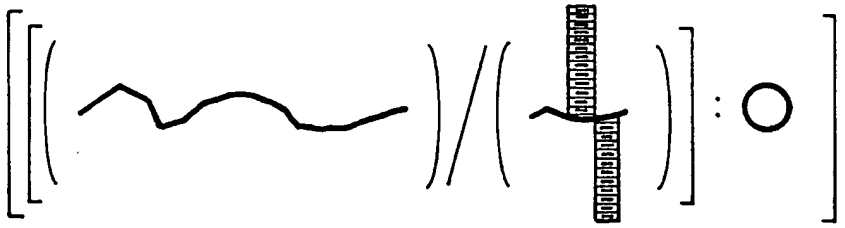
P0 - SEMICRYSTALLINE HOMOPOLYMERS, SEMICRYSTALLINE COPOLYMERS AND BLENDS THEREOF

P1 - THERMOPLASTIC ELASTOMERS WITH LINEAR CHAINS



P2- THERMOPLASTIC ELASTOMERS WITH SIDE CHAINS OR ANY KIND OF DENDRITIC STRUCTURAL ELEMENTS





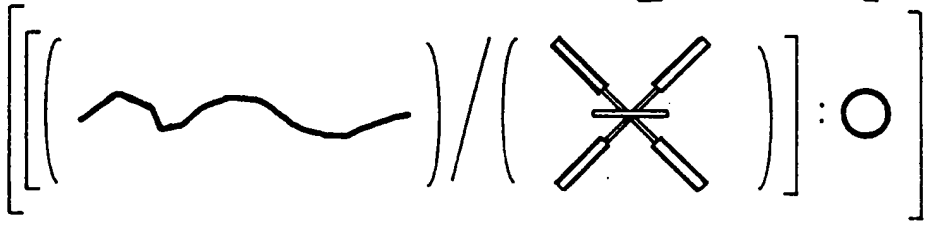


FIG. 3

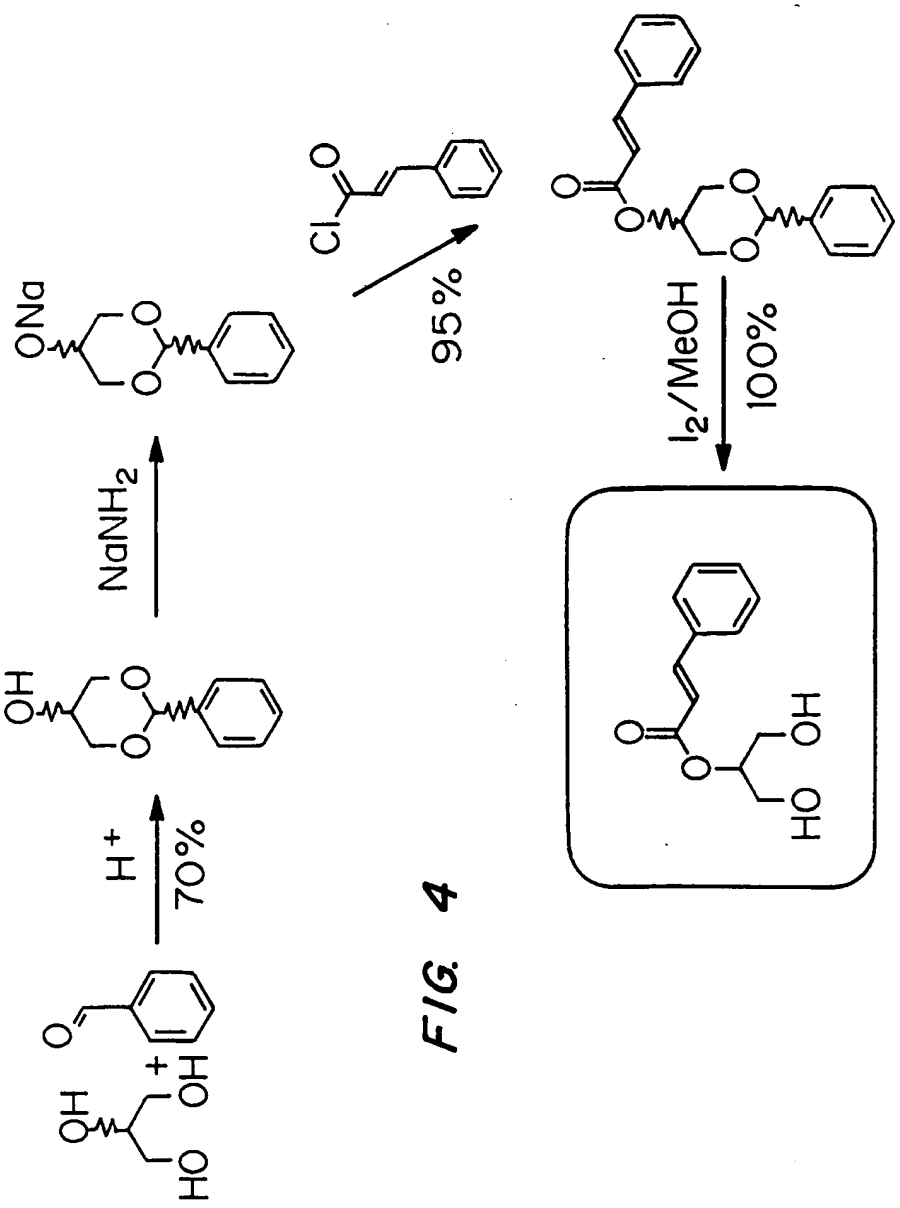


FIG. 4

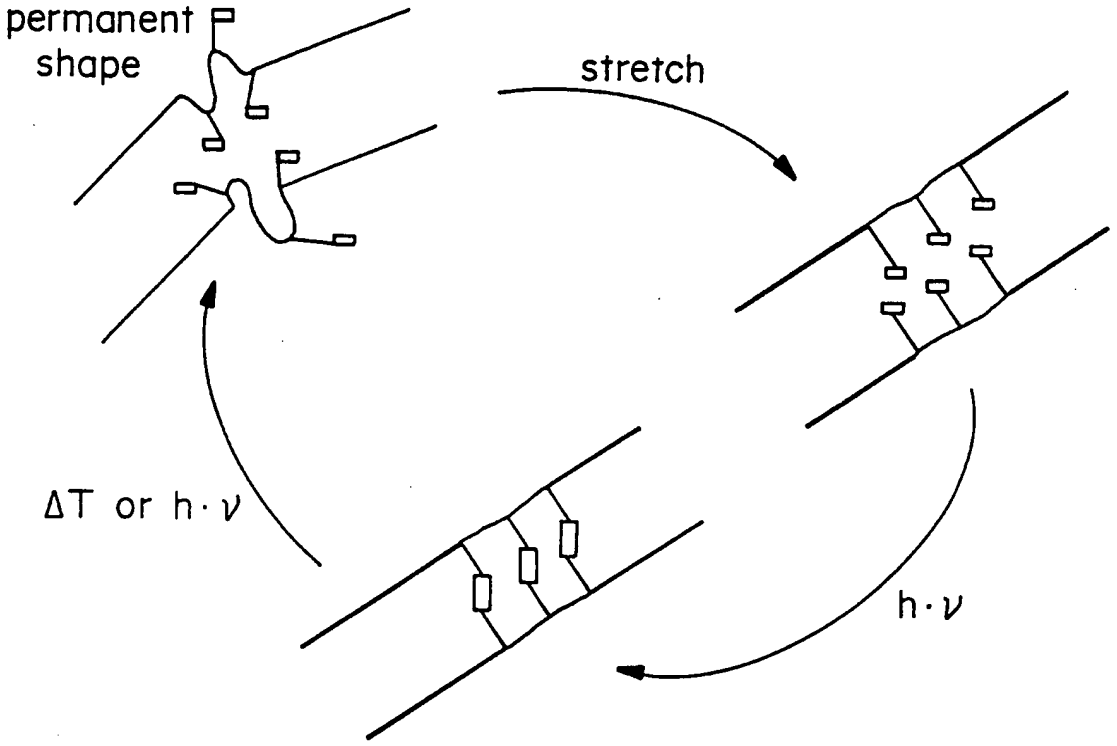

permanent shape
stretch
ΔT or h·ν
h·ν

FIG. 5

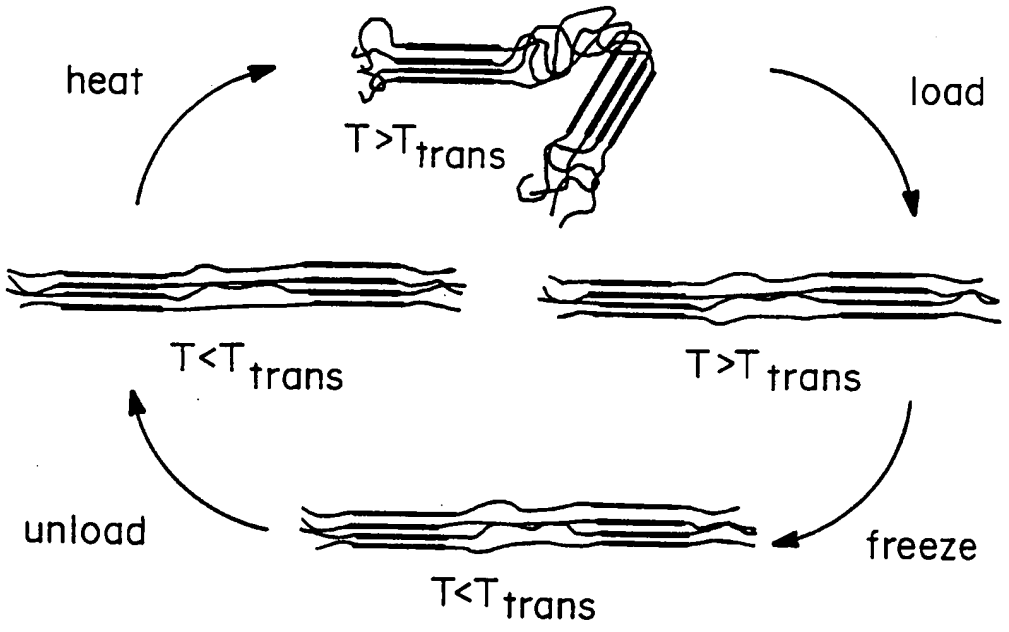

heat
T>T trans
load
T<T trans
T>T trans
unload
freeze
T<T trans

FIG. 6

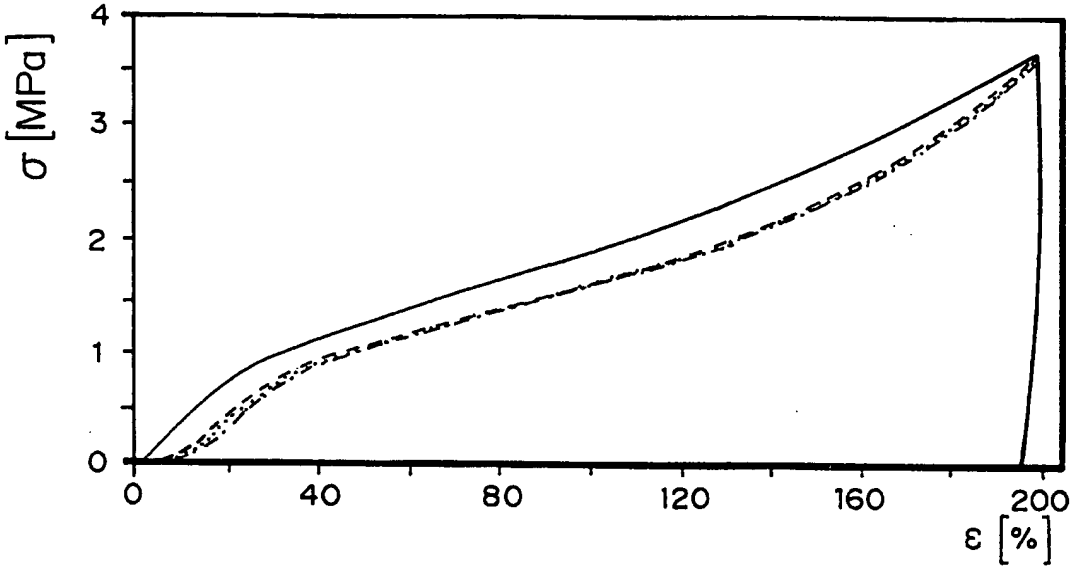

σ [MPa]
4
3
2
1
0
0
40
80
120
160
200
ε [%]

FIG. 7

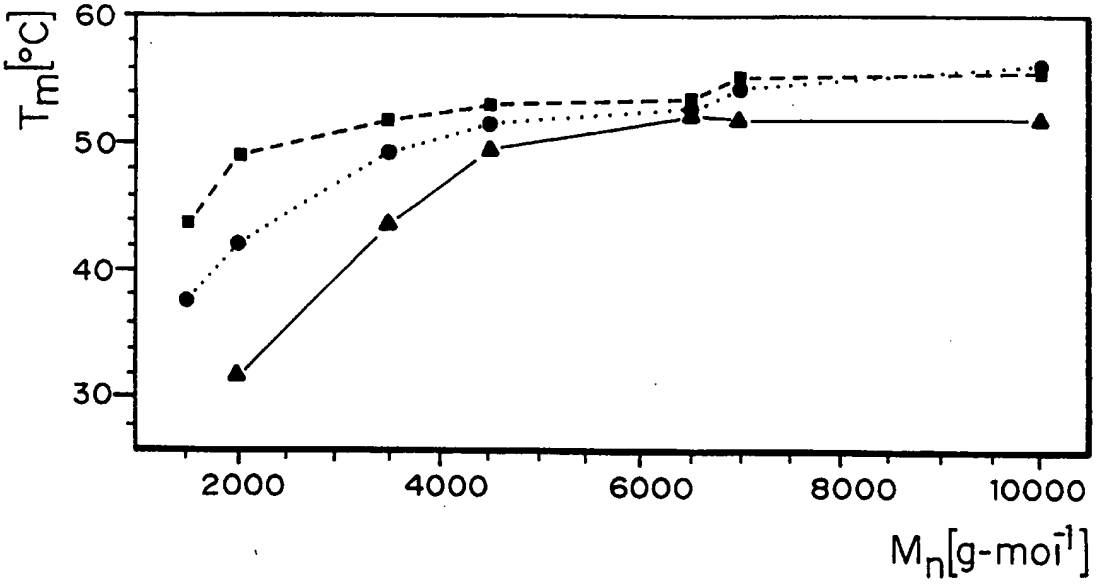

Tm[°C]
60
50
40
30
2000
4000
6000
8000
10000
Mn[g-moi-1]

FIG. 8

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 99/03977

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61L27/00 A61L29/00 A61L31/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61L

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 326 426 A (JAPAN MEDICAL SUPPLY CO., LTD.) 2 August 1989 see page 2, line 25 - line 31; claims 1,5	1,9-12, 21-25
X	WO 95 34331 A (AO FORSCHUNGSINST ;GOGOLEWSKI SYLWESTER (CH); GANZ RHEINOLD (CH)) 21 December 1995 see page 5, line 19 - line 22; claims 8,10	1,9, 21-25
A	DE 42 26 465 A (GUNZE LTD.) 11 February 1993 see claims 1,3	1,10-12, 19,21-25

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
8 June 1999	15/06/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Angiolini, D

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int. ational Appl[illegible]n No
PCT/US 99/03977

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 326426 A	02-08-1989	JP 1192367 A	02-08-1989
		JP 2561853 B	11-12-1996
		CA 1307885 A	29-09-1992
		DE 68920055 D	02-02-1995
		DE 68920055 T	11-05-1995
		US 4950258 A	21-08-1990
WO 9534331 A	21-12-1995	NONE	
DE 4226465 A	11-02-1993	JP 5042202 A	23-02-1993
		JP 5309103 A	22-11-1993

Table 5: Gelation Times

Polymer	UV polymerization * gelation time (mean ±S.D.) (s)	Laser Polymerization** gelation time (s)
1KG	5.3±4.1	<1
4KG	14.7±0.5	<1
6KG	9.3±0.5	<1
10KG	18.±0.8	<1
10KL	7.7±0.5	<1
18KG	23.3±1.2	<1
20KG	13.3±0.5	<1

* Initiator: 2,2-dimethoxy-2-phenylacetophenone, concentration 900 ppm: 0.2 ml of 23% monomer solution in PBS

** Argon ion laser emitting at 514nm. power 3 W/cm^2: ethyloeosin, triethanol amine initiating system: 0.2 ml of 23% monomer solution in PBS

Biodegradability

Biodegradation of the resulting polymer network is an important criteria in many biomedical applications. Degradation of poly(glycolic acid and poly(DL-lactic acid) has been well documented in the literature. The degradation mainly takes place through the hydrolysis of the ester bond; the reaction is second order and highly pH dependent. The rate constant at pH 10 is 7 times faster than that at pH 7.2.

Such facile biodegradation is surprising because poly(α-hydroxyacidesters) are hydrophobic and highly insoluble in water. Accessibility of the polymer matrix to the aqueous surrounding is therefore limited. However, because the networks are hydrogels which are swollen with water, all the ester linkages in the network are in constant contact with water with the aqueous surroundings. This results in a uniform

bulk degradation rather than a surface degradation of these gels.

Table 6 gives hydrolysis data for some of these networks; times listed are for complete dissolution of 60 mg of gel at pH 7.2 and 9.6. As noted, most of the gels dissolve within 12 hours at pH 9.6. 18.5k gel dissolves within 2.5 hr at pH 9.6 whereas 18.5KCO gel does not dissolve in 3 days, indicating that the lactoyl, glycoloyl, or ε-caprolactoyl ester moiety is responsible for degradation of these networks. It also can be seen that the 18.5KG gel hydrolyzes more rapidly than the 4KG gel. This may be due to the reduced hydrophilicity and higher crosslink density of the latter gel.

Table 6: Hydrolysis Data

Oligomer used for gelation	Time taken to dissolve gel at pH 9.6 (h)	Time taken to dissolve gel at pH 7.2 (days)
4KG	6.2	5.5
10KG	12.25	5.5
18.5KG	2.25	>7
18.5KCL	>5 days	>7
18.5KCO	>5 days	>7

Characterization of macromers

FTIR spectra of the prepolymers were recorded on a DIGILAB model FTS 15/90. The absorption at 1110 cm^{-1} (characteristic C-O-C absorption of PEG) shows the presence of PEG segments. The strong 1760 cm^{-1} absorption shows the presence of glycolic ester. The absence of hydroxyl group absorption around 3400 cm^{-1} and a weak acrylic double bond absorption at 1590 cm^{-1} shows the presence of acrylic double bonds at the end groups.

500 MHz proton and 125 MHz carbon-13 spectra were recorded on a GE 500 instrument. The presence of a very strong peak at 4.9 ppm due to CH_2 methylene from the PEG segment, a peak at 5.09 ppm due to the

glycolic ester segment and an acrylic proton singlet at 5.8 ppm can be easily seen from proton NMR. The estimated molecular weight of PEG segment and glycolic acid segment for different copolymers is shown in Table 2. The carbonyl peak at 169.39 ppm from glycolic acid and 36.5 ppm peak from methylene carbons from PEG in carbon-13 NMR are consistent with the reported chemical composition of these copolymers.

Differential scanning calorimetry (Perkin Elmer DSC-7) was used to characterize the oligomers for thermal transitions. The oligomers were heated from -40°C to 200°C at a rate of 20°C/min, presumably causing polymerization. The polymer was then cooled to -40°C at a rate of 60°C/min and again heated to 200°C at a rate of 20°C/min. The first scans of biodegradable 18.5K PEG glycolide tetraacrylate (18.5KG) oligomer were compared to that of the non-degradable 18.5K PEG tetraacrylate (18.5KCO) scan. It was seen that a glass transition appears in the 18.5KG at -2°C while no such transition exists in the 18.5KCO. A small melting peak at 140°C was also evident due to the few glycolic acid mers which can crystallize to a limited extent. The melting peak for PEG is shifted downwards in 18.5KG to 57°C from 60.7°C for 18.5KCO. This is probably due to disturbance of the PEO crystalline structure due to the presence of the glycolic acid linkages. In the third cycle, by which time the oligomers have presumably polymerized, the Tg and Tm transitions for the glycolide segments can no longer be seen, indicating that a crosslinked network has formed and the glycolic acid segments are no longer capable of mobility.

The degree of polymerization (D.P.) of the degradable segments added to the central water soluble PEG chain was determined in several cases using ^{1}H NMR. The experimentally determined D.P. was seen to be in good agreement with the calculated number, as shown by

Figure 1A. Thus, the ring opening reaction initiated by the PEG hydroxyls proceeds to completion, giving quantitative yields.

Determination of Total Water, Free Water Bound Water

Solutions of various degradable macromers were made as described above. Gels in the shape of discs were made using a mold. 400 μl of solution was used for each disc. The solutions were irradiated for 2 minutes to ensure thorough gelation. The disc shaped gels were removed and dried under vacuum at 60°C for 2 days. The discs were weighed (W1) and then extracted repeatedly with chloroform for 1 day. The discs were dried again and weighed (W2). The gel fraction was calculated as W2/W1. This data appears in Table 7.

Subsequent to extraction, the discs were allowed to equilibrate with PBS for 6 hours and weighed (W3 after excess water had been carefully swabbed away). The total water content was calculated as (W3-W2) X 100/W3. Differential scanning calorimetry (DSC) was used to determine the amount of free water that was available in the gels. A scan rate of 20°C/min was used and the heat capacity for the endotherm for water melting was measured (H1). The heat capacity of HBS was also measured (H2). The fraction of free water was calculated as H1/H2. The residual water was assumed to be bound due to hydrogen bonding with the PEO segments. The presence of free water in the gels was indicated. This free water can be expected to help proteins and enzymes entrapped in such gels in maintaining their native conformation and reducing deactivation. Thus these gels would appear to be suited for controlled release of biological micromolecules. The data for gel water content is summarized in Table 7

Table 7: Hydrogel Water content

Polymer Code	% Free Water	% Bound Water	% Total Water	% Gel Content
1KG	68.4	14	82.3±2.6	61.3±5.2
4KG	78.0	9.3	87.3±1.8	56.3±0.9
6KG	74.8	13.4	88.1±3.3	66.5±2.35
10KG	83.7	10.8	94.5±0.5	54.3±0.6
10KL	82.0	9.7	91.7±0.5	63.9±3.7
18.5KG	71.8	22.3	94.0±0.4	47.0±4.9
20KG	79.8	14.8	94.5±0.4	44.5±4.8

Example 2: Use of multifunctional macromers.

30 g of a tetrafunctional water soluble PEG (MW 18,500) (PEG 18.5k) was dried by dissolving the polymer in benzene and distilling off the water benzene azeotrope. In a glove bag, 20 g of PEG 18.5 k, 1.881 g of glycolide and 15 mg of stannous octoate were charged into a 100 ml round bottom flask. The flask was capped with a vacuum stopcock, placed into a silicone oil bath and connected to a vacuum line. The temperature of the bath was raised to 200°C. The reaction was carried out for 4 hours at 200°C and 2 hours at 160°C. The reaction mixture was cooled, dissolved in dichloromethane and the copolymer was precipitated by pouring into an excess of dry ethyl ether. It was redissolved in 200 ml of dichloromethane in a 500 ml round bottom flask cooled to 0°C. To this flask, 0.854 g of triethylamine and 0.514 ml of acryloyl chloride were added under nitrogen atmosphere and the reaction mixture was stirred for 12 h. at 0°C. The triethyl amine hydrochloride was separated by filtration and the copolymer was recovered from filtrate by precipitating in diethyl ether. The polymer was dried at 50°C under vacuum for 1 day.

Example 3: Synthesis of a photosensitive macromer containing DL-lactide.

PEG (MW) 20,000) (PEG 20k) was dried by dissolving in benzene and distilling off the water benzene azeotrope. In a glove bag, 32.43 g of PEG 20k, 2.335 g of DL-lactide and 15 mg of stannous octoate were charged into a 100 ml round bottom flask. The flask was capped with a vacuum stopcock, placed into a silicone oil bath and connected to a vacuum line. The temperature of the bath was raised to 200°C. The reaction was carried out for 4 hours at 200°C. The reaction mixture was cooled, dissolved in dichloromethane and the copolymer was precipitated by pouring into an excess of dry ethyl ether. It was redissolved in 200 ml of dichloromethane in a 500 ml round bottom flask cooled to 0°C. To this flask, 0.854 g of triethylamine and 0.514 ml of acryloyl chloride were added under nitrogen atmosphere and the reaction mixture was stirred for 12 hours at 0°C. The triethyl amine hydrochloride was separated by filtration and the copolymer was recovered from filtrate by precipitating in diethyl ether. The polymer was dried at 50°C under vacuum for 1 day.

Example 4: Synthesis of a Photosensitive Precursor Containing DL-Lactide and ϵ-Caprolactone.

PEG (MW 600) (PEG 0.6k) was dried by dissolving in benzene and distilling off the water benzene azeotrope. In a glove bag, 0.973 g of PEG 0.6k, 0.467 g of DL-lactide along with 0.185 g of ϵ-caprolactone and 15 mg of stannous octoate were charged into a 50 ml round bottom flask. The flask was capped with a vacuum stopcock, placed into a silicone oil bath and connected to a vacuum line. The temperature of the bath was raised to 200°C. The reaction was carried out for 4 hours at 200°C and 2 hours at 160°C. The reaction mixture was cooled, dissolved in dichloromethane and the copolymer was precipitated by

pouring into an excess of dry ethyl ether. It was redissolved in 50 ml of dichloromethane in a 250 ml round bottom flask cooled to 0°C. to this flask, 0.854 g of triethylamine and 0.514 ml of acryloyl chloride were added under nitrogen atmosphere and the reaction mixture was stirred for 12 hours at 0°C. The triethyl amine hydrochloride was separated by filtration and the copolymer was recovered from filtrate by precipitating in diethyl ether. The polymer was dried at 50°C under vacuum for 1 day and was a liquid at room temperature.

Example 5: Selection of dyes for use in photopolymerization.

It is possible to initiate photopolymerization with a wide variety of dyes as initiators and a number of electron donors as effective cocatalysts. Table 8 illustrates photopolymerization initiated by several other dyes which have chromophores absorbing at widely different wavelengths. All gelations were carried out using a 23% w/w solution of 18.5KG in HEPES buffered saline. These initiating systems compare favorably with conventional thermal initiating systems, as can also be seen from Table 8. Other photoinitiators that may be particularly useful are 2-methoxy-2-phenyl acetophenone and camphorquinone.

Table 8: Polymerization Initiation of 18.5KG PEG

INITIATOR	LIGHT SOURCE*	TEMPERATURE °C	GEL TIME (SEC)
Eosin Y, 0.00015M; Triethanolamine 0.65M	S1 with UV filter	25	10
Eosin Y, 0.00015M; Triethanolamine 0.65M	S4	25	0.1
Methylene Blue, 0.00024M; p-toluenesulfinic acid, 0.0048M	S3	25	120
2,2-dimethoxy-2-phenyl acetophenone 900 ppm	S2	25	8
Potassium persulfate 0.0168M	-	75	180
Potassium Persulfate 0.0168M; tetramethyl ethylene-diamine 0.039M	-	25	120
Tetramethyl ethylene-diamine 0.039M; Riboflavin 0.00047M	S1 with UV filter	25	300

***LIST OF LIGHT SOURCES USED**

CODE SOURCE

S1 Mercury lamp, LEITZ WETSLER Type 307-148.002, 100W

S2 Black Ray longwave UV lamp, model B-100A W/FLOOD

S3 MELLES GRIOT He-Ne laser, 10mW output, 1=632 nm

S4 American laser corporation, argon ion laser, model 909BP-15-01001; λ=488 and 514 nm

Numerous other dyes can be used for photopolymerization. These dyes include but are not limited to: Erythrosin, phloxine, rose bengal, thioneine, camphorquinone, ethyl eosin, eosin, methylene blue, and riboflavin. The several possible cocatalysts that can be used include but are not limited to: N-methyl diethanolamine, N,N-dimethyl benzylamine, triethanol amine, triethylamine, dibenzyl

amine, N-benzyl ethanolamine, N-isopropyl benzylamine, and N-vinyl pyrrolidinone.

Example 6: Thermosensitive Biodegradable Gels from N-Isopropyl Acrylamide.

Synthesis of low molecular weight polyisopropyl acrylamide.

N-isopropyl acrylamide (NIPAAm) was recrystallized from 65:35 hexane benzene mixture. Azobisisobutyronitrile (AIBN) was recrystallized from methanol. 1.5 g of NIPAAm was polymerized using 3 mg of AIBN and 150 mg of mercaptoethanol in 1:1 acetone water mixture (24 hours at 65°C). The viscous liquid after polymerization was purified by dissolving in acetone and precipitating in diethyl ether. Yield 80%.

This hydroxy terminated low molecular weight poly(NIPAAm) was used in chain extension reactions using glycolide and subsequent endcapping reaction using acryloyl chloride as described in other examples.

1 g of modified poly(NIPAAm) based oligomer and 0.2 g 1KL were dissolved in water at 0°C and polymerized at 0°C using 2-2-dimethoxy-2-phenylacetophenone (900 PPM).

Example 7: *In Vitro* Degradation

The gels were extracted as described in Example 1 to remove the unpolymerized macromer fraction fraction and the gels were then placed in 50 mM HEPES buffered saline (0.9% NaCl), pH 7.4 at 37°C. Duplicate samples were periodically removed, washed with fresh HBS and dried at 100°C for 1 day and weighed to determine mass loss in the gel. The compositions of the various gels used were the same as described in the previous examples. Table 9 shows the extent of degradation of these gels given as percent of mass lost over time. The respective times are given in parenthesis along with the mass loss data.

Table 9: Gel Degradation

1KG	20.1% (1 d), 20.36±0.6 (2d), 21.7± (6d), 28.8±16.6 (10 d) estimated total Degradation time 45 days.
4KG	38.9 (1d), 60.3±4.2 (2d), 78.9 (3d), 99.3±4.7 (6d). Total degradation time 5.5 days.
6KG	18.3±6.8 (1d), 27.4±1.0 (2d), 32.8±11.3 (3d), 104.8±3.2 (5d). total degradation time 4.5 days 10KG 0.6±0.6 (8 hr), 100 (1d). Total degradation time 1 day.
10KL	10.0±4.84 (2d), 6.8±1.7 (3d), 4.5±3.1 (6d), 8.0±0.2 (10d). Total degradation time estimated to be 20 days.
20KG	68.1±4.2 (8hr), 99.7±0.3 (1d). Total degradation time 15 hr.

Example 8: Fibroblast adhesion and spreading.

The *in vitro* response of Human foreskin fibroblast (HFF) cells to photopolymerized gels was evaluated through cell culture on polymer networks. 0.2 ml of monomer solution was UV polymerized on an 18 x 18 mm glass coverslips under sterile conditions. HFF cells were seeded on these gels at a cell density of 1.8×10^4 cells/sq cm of coverslip area in Dulbecco's Modified Eagle's Medium (DMEM) supplemented with 10% fetal calf serum. The gels were incubated for 6 hr at 37°C in a 5% CO_2 environment, at the end of which they were washed twice with phosphate buffered saline (PBS). The adherent cells were fixed using a 2% glutaraldehyde solution in PBS. The gels were examined under a phase contrast microscope at a magnification of 200X, and the number of adherent and spread cells evaluated by examining five fields selected at predetermined locations on the coverslips.

The number of adherent cells is reported in Table 10 along with those for glass control surfaces.

Cell adhesion is seen to be dramatically lowered on gel-coated glass.

Table 10: Cell Adhesion

Surface	**Attached Cells/cm^2**
glass	13220±3730
18.5KG	250±240
18.5KCL	1170±1020
18.5KCO	390±150

Typical photographs of these cells on the 18.5KCL gel surfaces and on control glass surfaces are shown in Figures 2A and 2B. It can be easily seen from Table 10 that these gels are highly resistant to cellular growth. Even the 18.5KCL is still less than 10% of the glass. Cells attached to the glass surface show a flattened and well-spread morphology whereas the few cells that are attached to the gel are rounded and loosely attached. This may result from the fact that hydrated PEG chains have a high motility and have been shown to be effective in minimizing protein adsorption. One of the mechanisms by which cell adhesion is mediated is through the interaction of cell surface receptors with adsorbed cell adhesion proteins. Thus the reduction in overall protein adsorption results in minimal cell adhesion protein adsorption and reduced cell adhesion.

Example 9: Release of Protein (Bovine Serum Albumin) from Polymers.

1KG was used for this study. This macromer was liquid at room temperature and was used as such. 1 mg of bovine serum albumin (BSA) was added per ml of monomer solution along with 0.9 mg/ml of 2,2-dimethoxy-2-phenyl-acetophenone as initiator. The protein was dissolved in the monomer solution and disc shaped gels were made by exposing 0.2 g of macromer mixture to LWUV for 1 min. Two such discs were placed in a flask containing 20 ml of PBS and incubated at 37°C. Two aliquots of 20 μl each were removed from

these flasks periodically and the amount of BSA released was assayed using the Bio-Rad total protein assay. The release profile for BSA is shown in Figure 3A. It can be seen that the release of BSA is relatively steady over more than a month.

Example 10: Enzyme Release Assay

Water solubility of the macromers means gelation can be carried out in a non-toxic environment. This makes these materials suitable for intraoperative uses where *in situ* gelation is needed. Since the precursors are water soluble, the gels can be used as drug delivery vehicles for water soluble drugs, especially macromolecular drugs such as enzymes, which would otherwise be denatured and lose their activity. Release of lysosome and tPA from the polymers was used to illustrate the feasibility of using biodegradable hydrogels for controlled release of biomolecules.

Lysozyme release

The enzyme lysozyme (MW:14,400) is a convenient model for release of a low molecular weight protein from a biodegradable gel. The Biorad total protein assay was used to quantify the enzyme released. The enzyme was dissolved in PBS at a concentration of 20 mg/ml. The monomer PEG-dl-lactic acid-diacrylate was dissolved in PBS to produce a 40% solution. The lysozyme solution was added to the monomer solution to attain a 24% monomer solution. The monomer/lysozyme solution was polymerized under UV in a cylindrical mold, using 30 μl of the initiator 2,2-dimethoxy-2-phenyl-acetophenone in 1-vinyl-2-pyrrolidone (30 mg/ml) as the initiator. The polymer was cut into 10 equal sized pieces and immersed in 10 ml PBS. Samples of the PBS were withdrawn at intervals and assayed for lysozyme released into the PBS. Lysozyme was released from the PEG-DL-lactic acid-diacrylate gel over an 8 day interval, with the maximum rate of release

occurring within the first 2 days, as shown by Figure 3B.

Release of recombinant t-PA

Three macromers were used for these studies: 1KL, 4KG, and 18.5KG. The 1KL macromer was liquid at room temperature and was used as such. The second macromer, 4KG, was used as a 75% w/w solution in PBS. The third composition was a mixture of equal parts of 1KL and a 50% w/w solution of 18.5KG. 3.37 mg of tissue plasminogen activator (single chain, recombinant, M.W. 71,000) was added per gram of macromer solution along with 0.9 mg/ml of 2,2 dimethoxy 2 phenyl acetophenone as initiator. The protein was dissolved with the macromer and disc shaped gels were made by exposing 0.2 g of macromer mixture to LWUV for 1 minute. Two such discs were rinsed with PBS, placed in a flask containing 5 ml of PBS and incubated at 37°C. Two aliquots of 100 μl each were removed from these flasks periodically and the amount of active t-PA released was assayed using a chromogenic substrate assay (Kabi-vitrum). The release profiles from the 1K lactide gels, 4K glycolide gels, and the 50/50 1K glycolide/18.5K glycolide are shown in Figures 4A - 4C. Fully active tPA can be released for periods up to at least two months.

By selecting an appropriate formulation, the release rate can be tailored for a particular application. It is also possible to combine formulations with different molecular weights so as to synergistically achieve appropriate attributes in release and mechanical characteristics.

For prevention of postoperative adhesions, in addition to the barrier effect of the gels, the gels can be loaded with a fibrinolytic agent to lyse incipient filmy adhesions which escape the barrier

effect. This further enhances the efficacy of biodegradable gels in adhesion prevention.

Example 11: Toxicity of Polymers and Commercial Adhesives.

To evaluate the toxicity of *in situ* polymerization of the macromer solutions described herein, as compared to commercial adhesives, 100 μl of 18.5KCO prepolymer solution was placed on the right lobe of a rat liver and gelled by exposing it to LWUV for 15 sec; similarly, a few drops of a n-butyl cyanoacrylate based glue were placed on the left lobe. The liver was excised after a week, fixed in 10% neutral buffered formalin, blocked in paraffin, sectioned and stained using hematoxylin and eosin.

No adverse tissue reaction was evident on the surface of the lobe exposed to the biodegradable gel. No inflammatory reaction to the polymerization process can be seen. The epithelium looks normal, with no foreign body reaction.

In comparison, the lobe exposed to cyanoacrylate glue shows extensive tissue necrosis and scarring with 10-30 cell deep necrotic tissue. Fibrosis is evident in the necrotic portions close to underlying normal tissue.

Example 12: Prevention of Post-Surgical Adhesions with Photopolymerized Biodegradable Polymer.

A viscous sterile 23% solution in phosphate buffered saline (8.0 g/l NaCl, 0.201 g/l KCl, 0.611 g/l Na_2HPO_4, 0.191 g/l KH_2PO_4, pH 7.4) of polyethylene glycol (M.W. 18,500) which has been chain extended on both ends with a short polyglycolide repeat unit (average number of glycolidyl residues: 10 on each end) and which has been subsequently terminated with an acrylate group was prepared. Initiator needed for the crosslinking reaction, 2,2-dimethoxy-2-phenyl acetophenone, was added to the macromer solution to

achieve an initiator concentration of 900 ppm. A 30 second exposure to a long wave UV lamp (Blak Ray) is sufficient to cause polymerization.

Animal models evaluated

Animal models evaluated included a rat cecum model and a rabbit uterine horm model. In the rat cecum mode, 6 out of 7 animals treated with the macromer solution showed no adhesions whatsoever, while untreated animals showed consistent dense adhesion formation. In the rabbit uterine horn model, a significant ($p<0.01$) reduction in adhesion formation was seen in the animals treated with the gel. Studies conducted in rats using only the ungelled viscous precursor solution (no LWUV) failed to prevent the formation of adhesions.

Rat cecum model

Twenty-one Sprague Dawley male rats having an average weight of 250 gm were divided into three groups for treatment and two for controls. The abdomen was shaved and prepared with a betadine solution. A midline incision was made under Equithesin anesthesia. The cecum was located and 4 to 5 scrapes were made on a region about 2 x 1 cm on one side of the cecum, using a 4 x 4 in gauze pad to produce serosal injury and punctate bleeding. The abdominal incisions in these animals were closed using a continuous 4-0 silk suture for the musculoperitoneal layer and 7.5 mm stainless steel staples for the cutaneous layer. A topical antibiotic was applied at the incision site.

The first group consisted of 7 animals serving as controls without treatment, to confirm the validity of the model. The second group served as a control with the application of the precursor but without photopolymerization to form the hydrogel. After induction of the cecal injury, about 0.25 ml of the precursor solution was applied to the injury site

using a pipet. The abdominal incision was then closed as above.

The third group served as the gel treatment group and was prepared as the second group except that the precursor film was exposed to a LWUV lamp for 45 seconds to cause gelation. Both the obverse and reverse sides of the cecum were similarly treated with precursor and light. No attempt was made to dry the surface of the tissue, to remove blood, or to irrigate the area prior to treatment.

The animals were sacrificed at the end of two weeks by CO_2 asphyxiation. The incisions were reopened and adhesions were scored for location, extent, and tenacity. The extent of adhesions was reported as a percentage of the traumatized area of the cecum which forms adhesions with adnexal organs or the peritoneal wall. Tenacity of the adhesions was scored on a scale from 0 to 4: no adhesions - grade 0; tentative transparent adhesions which frequently separate on their own - grade 1; adhesions that give some resistance but can be separated by hand - grade 2; adhesions that require blunt instrument dissection to separate - grade 3; and dense thick adhesions which require sharp instrument dissection in the plane of the adhesion to separate -grade 4.

Rat cecum model results

The control group without treatment shows consistently dense and extensive adhesions. The extent of abraded area covered with adhesions was seen to be 73±21% (mean ± S.D., n=7). The severity of adhesions was grade 3.5±0.4. Most of the adhesions were dense and fibrous, involving the cecum with itself, with the peritoneal wall and with other organs such as the liver, small intestine, and large intestine. Frequently the nesentery was seen to be involved in adhesions. In the control group with the application of precursor solution but without gelation

by exposure to the LWUV lamp, the extent of adhesion was 60 ± 24% (n=7), and the severity of adhesions was 3.1 ± 0.4. In the gel treated group, the cecum was seen to be completely free of adhesions in 6 out of 7 animals. In one case, a grade 2 adhesion was seen with the mesentery over 10% of the area and a grade 2.5 adhesion was seen over 15% of the area, bridging the cecum to the sutures on the site of the incision in the peritoneal wall. The overall adhesion extent for the group was 4%, and the overall severity was 0.32. No evidence of residual gel was visible, the gel presumably having degraded within the prior two weeks. The cecum appeared whitish with a fibrous layer on the surface in the control group, but the tissue appeared healthy and normal in animals treated with the gel.

Rabbit uterine horn model

Eight sexually mature female New Zealand rabbits between 2 and 3 kg in weight were prepared for surgery. A midline incision was made in the lower abdominal region under Rompun, Ketamine, and Acepromazine anesthesia. The uterine horns were located and the vasculature to both horns was systematically cauterized to induce an ischemic injury. One animal was rejected from the study due to immature uterine horns. Seven rabbits were selected for the treatment with only the photopolymerizable hydrogel and two animals were selected for evaluating the combined efficacy of the hydrogel with a fibrinolytic agent, tissue plasminogen activator (tPA). 5 mg of tPA/ml macromer solution was used in the latter case. After cauterization, macromer solutions (0.5 ml) were applied along the horn and allowed to coat the surface where the cauterization injury had been induced. After uniform application of the solution was complete, the horns were exposed to a LWUV lamp for 1 min to induce gelation. The procedure

was repeated on the reverse side of the horns. The incisions were then closed using a continuous 2-0 Vicryl (Ethicon) suture for the musculoperitoneal layer and a 0 Vicryl (Ethicon) suture for the cutaneous layer. No prophylactic antibiotics were administered. No postoperative complications or infections were observed. Five animals were used in the control group. The ischemic injury was made as described and the incision was closed without the application of the precursor; all techniques were identical between the treatment group and the control group.

Controls were used where the same animal model was subjected to surgery without application of the macromer; all surgical techniques were identical between the treatment group and the historical controls.

The rabbits were reoperated under Ketamine anesthesia at the end of two weeks to evaluate adhesion formation; they were sacrificed by introcardiac KCl injection. Adhesion formation was evaluated for extent and tenacity. Extent of adhesion formation was evaluated by measuring the length of the uterine horn that formed adhesions with itself or with the peritoneal wall or other organs. Tenacity of adhesion was classified as either filmy or fibrous. Filmy adhesions were usually transparent, less strong, and could be freed by hand. The fibrous adhesions were dense, whitish, and usually required sharp instrument dissection to be freed. In cases where only a single filmy adhesion band was evident, a score of 5% was assigned.

Typical samples of the horn were excised for histology and were fixed in a 10% neutral buffered formalin solution. Paraffin sections of the samples were stained using hematoxylin and eosin.

Rabbit uterine horn model results

The adhesion score is the % of affected area occupied by the adhesions, with grading of each as being filmy or fibrous. Distorted horn anatomies were observed in control animals. The mean score in the control group was 50 ± 15% of the affected area of the horn being occupied by adhesions with 10% of these being filmy and 90% fibrous. Distorted horn anatomies were observed, as can be seen from Figure 5A which presents a superior view of the uterine horn in an animal used as a control, which showed adhesions over 66% of the horn surface. The group of animals treated only with the photopolymerized macromer showed an adhesion score of 13±11.4% (n=10). Of these, 4 animals showed less than 5% adhesions with only an occasional filmy band visible.

The animals treated with photopolymerized gel containing tPA showed further improved results over the "gel only" animals. One animals showed a filmy band on both the right and left horn. They were assigned a score of 5% with a total score of 10%. The other animal did not show any adhesions at all. Thus the total score for these animals was 5±5%.

Figure 5B shows normal horn anatomy in a typical horn which has undergone gel treatment. Adhesions are filmy in all cases and no dense bands are seen. No traces of the remaining gel could be observed. Typical samples of horns showing filmy adhesions showed some fibrous tissue with a 6-15 cell thick layer of fibroblasts showing some collagen fibrils but no formation of dense collagen fibers. The horns showing no adhesions occasionally showed a 1-4 cell thick layer of fibroblasts, but mostly a normal epithelium with no evidence of inflammatory cells.

This same procedure was slightly modified as described below as a better mode of using the polymers

to prevent postoperative adhesions using the rat uterine horn model.

Female rats were anesthetized with pentobarbital (50 mg/kg, intraperitoneally), and a midline laparotomy was performed. The uterine horns were exposed, and the vasculature in the arcade feeding the horns was systematically cauterized using bipolar cautery; the most proximal and most distal large vessel on each horn were not cauterized. Following this, the antimesenteric surface of each horn was cauterized at two 1 mm diameter spots on each horn, each separated by a 2 cm distance, the pair centered along the length of each horn. Following injury, 0.5 ml of macromer solution was applied per horn and was gelled by exposure to long wavelength ultraviolet light (365 nm, approximately 20 mW/cm^2) for 15 sec per surface on the front side and on the back side each. The uterus was replaced in the peritoneal cavity, and the musculoperitoneal and skin layers were closed.

The macromer consisted of a PEG chain of MW 8,000 daltons, extended on both sides with a lactic acid oligomer of an average degree of polymerization of 5 lactidyl groups, and further acrylated nominally at both ends by reaction with acryloyl chloride. In one batch, Batch A, the degree of acrylation was determined by NMR to be approximately 75%, and in another, Batch B, it was determined to be greater than approximately 95%. The macromer was dissolved in saline at a specified concentration, and the initiation system used was 2,2-dimethoxy-2-phenyl acetophenone from a stock solution in N-vinyl pyrrolidinone, the final concentration of 2,2-dimethoxy-2-phenyl acetophenone being 900 ppm and the final concentration of N-vinyl pyrrolidinone being 0.15%.

In one set of experiments, macromer from Batch A was applied in varying concentrations, and adhesions

were scored at 7 days postoperatively. Scoring was performed by two means. The length of the horns involved in adhesions was measured with a ruler, and the fraction of the total length was calculated. The nature of the adhesions was also scored on a subjective scale, 0 being no adhesions, 1 being filmy adhesions that are easily separated by hand, and 2 being dense adhesions that can only be separated by sharp instrument dissection. Furthermore, one of the samples contained tissue-plasminogen activator (t-PA), which is known to reduce adhesions, at a concentration of 0.5 mg/ml (0.5%) macromer solution. The results are shown in Table 11 for macromer batch A and batch B.

In a third set of experiments, adhesions were formed in female rats as described above, and the adhesions were surgically lysed 7 days after the initial surgery. The extent and grade of adhesions was scored during lysis. The animals were divided into two groups, and one group was treated with macromer from Batch B at a concentration of 10%. The results are shown in Table 11 as batch B, 10%.

Table 11: Reduction of Adhesions with Polymer.

Concentration macromer	Extent of adhesions % (S.D.)	Grade of adhesions (0-2)	Number of Animals
Polymer A			
15%	24.6 (3.1)	1.1 (0.1)	7
20%	33.6 (9.8)	1.2 (0.3)	7
25%	37.5 (11.1)	1.2 (0.1)	7
30%	54.2 (12.0)	1.6 (0.4)	6
20% + t-PA	18.3 (6.4)	1.1 (0.1)	6
Control (saline)	72.6 (18.7)	1.5 (0.2)	7
Polymer B			
5%	22.1 (4.2)	1.2 (0.1)	7
10%	10.0 (5.1)	1.0(0)	7
15%	17.8 (5.7)	1.0 (0)	7
20%	26.3 (11.4)	1.4 (0.2)	7
Control (saline)	75.9 (4.4)	1.8 (0.3)	7

Polymer B, 10%

Scoring performed at:	group that became:			
time of lysis	Controls	85.9 (9.7)	1.8 (0.1)	7
Time of lysis	Treatment	79.4 (6.8)	1.7 (0.2)	7
7 days post-lysis	Controls	78.8 (11.3)	1.8 (0.1)	7
7 days post-lysis	Treatment	28.2 (5.1)	1.0 (0)	7

The above results illustrate that the photopolymerized macromer can reduce or prevent post operative adhesions in both primary adhesions and adhesiolysis models, and moreover that the gel can be used to locally release a drug to exert a combined beneficial effect.

Example 13: Nerve anastomosis.

The sciatic nerve of a rat was aseptically severed using a scalpel and allowed to pull apart. The two ends of the nerve were reopposed using sterile forceps, and a 50% solution in buffer of polymer 1KL,

a macromer made from PEG 1K with lactide chain extension and acrylate termination, with 0.1% 2,2-dimethoxy-2-phenoxy acetophenone was applied to the nerve stumps. The affected area was illuminated with a 100 W LWUV lamp for 60 seconds, and an adhesive bond was observed to form between the proximal and distal nerve stumps.

To ensure the biocompatibility of the applied material with the nerve tissue, the same solution of macromer was applied to nonsevered rat sciatic nerves, and the area of the incision was closed using standard small animal surgical technique. The area was reopened at 1 hour or 24 hour postoperatively, and the affected area of the nerve was removed en block and prepared for transmission electron microscopy. No morphological differences were observable between the treated nerves at either time point as compared to control rat sciatic nerves that were otherwise nonmanipulated, even though they had been traumatized and manipulated.

Example 14: Evaluation of PEG Based Degradable Gels as Tissue Adhesives.

Abdominal muscle flaps from female New Zealand white rabbits were excised and cut into strips 1 cm X 5 cm. The flaps were approximately 0.5 to 0.8 cm thick. A lap joint, 1 cm X 1 cm, was made using two such flaps. Two different compositions, 0.6KL and 1 KL, were evaluated on these tissues. Both these compositions were viscous liquids and were used without further dilution. 125 μl of ethyl eosin solution in N-vinyl pyrrolidone (20 mg/ml) along with 50 μl of triethanolamine was added to each ml of the adhesive solution. 100 μl of adhesive solution was applied to each of the overlapping flaps. The lap joint was then irradiated by scanning with a 2 W argon ion laser for 30 sec from each side. The strength of the resulting joints was evaluated by measuring the

force required to shear the lap joint. One end of the lap joint was clamped and an increasing load was applied to the other end, while holding the joint was clamped and an increasing load was applied to the other end, while holding the joint horizontally until it failed. Four joints were tested for each composition. The 1KL joints had a strength of 6.6±1.0 KPa (mean ±S.D.), while the 0.6KL joints had a strength of 11.4±2.9KPa. It is significant to note that it was possible to achieve photopolymerization and reasonable joint strength despite the 6-8 mm thickness of tissue. A spectrophotometric estimate using 514 nm light showed less than 1% transmission through such muscle tissue.

Example 15: Coupling of Photopolymerizable Groups to Proteins (Albumin).

PEG (M.W. 2,000) monoacrylate (5g) was dissolved in 20 ml dichloromethane. Triethyl amine (0.523 g) and 2,2,2-trifluoroethanesulfonyl chloride (tresyl chloride) (0.017 g) were added and the reaction was allowed to proceed for 3 hours at 0°C under nitrogen atmosphere. The reaction mixture was then filtered and the dichloromethane evaporated to dryness. The residue was redissolved in a small amount of dichloromethane and precipitated in diethyl ether. The polymer was then filtered and dried under vacuum for 10 hours and used directly in the subsequent reaction with albumin.

1 g of bovine serum albumin was dissolved in 200 ml of sodium bicarbonate buffer at pH 9. Tresyl activated PEG monoacrylate (5 g) was added and the reaction was stirred for 24 hours at 25°C. Albumin was separated by pouring the reaction mixture into acetone. It was further purified by dialysis using a 15,000 daltons cutoff dialysis membrane. A 10% w/v solution of the PEG acrylated albumin could be photopolymerized with long wave UV radiation using 0.9

mg/ml of 2,2 dimethoxy 2 phenylacetophenone as the initiator. In this gel the degradable segment is the protein albumin.

Example 16: Modification of Polysaccharides (Hyaluronic Acid)

In a dry 250 ml round bottom flask, 10 grams of PEG 400 monomethacrylate was dissolved in 100 ml dry dioxane, to which 4.053 g of carbonyl diimidazole (CDI) was slowly introduced under nitrogen atmosphere and the flask was heated to 50°C for 6 h. Thereafter the solvent was evaporated under vacuum and the CDI activated PEG monomer was purified by dissolving in dichloromethane and precipitating in ether twice.

1 g of hyaluronic acid, 5 g of CDI activated PEG 400 monoacrylate were dissolved in 200 ml sodium borate buffer (pH 8.5) and the solution was stirred for 24 hours. It was then dialyzed using a 15,000 dalton cutoff dialysis membrane to remove unreacted PEG. A 10% w/v solution of the acrylated hyaluronic acid was photopolymerized with long wave UV radiation, using 0.9 mg/ml of 2,2-dimethoxy-2-phenylacetophenone as the initiator. In this gel, the degradable region is hyaluronic acid.

Example 17: PEG Chain Extended with Polyorthocarbonates and Capped with Urethane Methacrylate.

3, 9-bis(methylene) 2,4,8,10-tetraoxaspiro [5,5] undecane (1g) and polyethylene glycol (molecular weight, 1,000, 7.059 g) were weighed into a 250 ml Schlenk tube under dry nitrogen atmosphere in a glove bag. 50 ml of dry tetrahydrofuran was introduced under nitrogen atmosphere and reaction mixture was stirred for 6 hours at 50°C. This is a typical step growth reaction with a disturbed stoichiometry, resulting in low molecular weight poloyorthocarbonate with terminal hydroxy groups. The oligomer was separated by precipitating in hexane and dried under

vacuum. 5 g of oligomer was redissolved in dry THF to which 20 μl of dibutyltindilaurate and 2 ml of 2-isocyanatoethyl methacrylate were slowly introduced and temperature was raised to 50°C. It was held there for 6 hours and cooled. The product was separated by precipitation in hexane. In this gel, the degradable region is a polyorthocarbonate.

Example 18: Microencapsulation of Animal Cells.

A 23% w/w solution of 18.5KG in HEPES buffered saline (5 ml) was used to resuspend 10^6 CEM-SS cells. Ethyl eosin (10^{-4} M) was used as a solution in N-vinyl pyrrolidone as the initiator and triethanolamine (0.01 M) was used as the coinitiator. The solution was then exposed through a coextrusion apparatus to an argon ion laser (514 nm, 2 Watts). The coextrusion apparatus had mineral oil as the fluid flowing annularly (flow rate 4 ml/min) around an extruding stream of the precursor cell suspension (flow rate 0.5 ml/min). The microdriplets gelled rapidly on being exposed to the laser light and were collected in a container containing PBS. The oil separated from the aqueous phase and the microspheres could be collected in the PBS below. The microspheres formed were thoroughly washed with PBS buffer to remove unreacted monomer and residual initiator. The size and shape of microspheres was dependent on extrusion rate and extruding capillary diameter (18 Ga to 25 Ga). The polymerization times were dependent on initiator concentration (ethyl eosin 5 μM to 0.5 mM, vinyl pyrrolidone (0.001% to 0.1%), and triethanolamine (5 mM to 0.1 M), laser power (120 mW to 2W), and monomer concentration (>10%w/v). Spheres prepared using this method had a diameter from 500 μm to 1,200 μm. The polymerizations were carried out at physiological pH in the presence of air. This is significant since radical polymerizations may be affected by the presence of oxygen. Cell viability subsequent to

encapsulation was checked by trypan blue exclusion assay and the encapsulated cells were found to be more than 95% viable after encapsulation.

Example 19: Various Formulations for the Prevention of Post Operative Adhesions.

The utility of PEG-oligo(α-hydroxy acid) diacrylates and tetraacrylates to prevent postoperative adhesions was evaluated in the rabbit uterine horn model as described above. The following polymers were synthesized, as described above: PEG 6K lactide diacrylate (6KL), PEG 10K lactide diacrylate (10KL). PEG 18.5K lactide (18.5KL), PEG 20K lactide (20KL). Solutions with 24% polymer in PBS with 900 ppm 2,2-dimethoxy-2-phenyl acetophenone, were prepared as described above. The solutions were applied to the uterine horn after cautery of the vascular arcade and illuminated with a 365 nm LWUV lamp, as described above. In one formulation, 18.5KL, 5 mg t-PA was mixed into the solution before application. Controls consisted of animals manipulated and cauterized but not treated with macromer solution. Measurement was performed on the 14th ± 1 day. Extent of adhesion was estimated from the fraction of the horn that was involved in adhesions, and the tenacity of adhesions was scored as 0, no adhesions; 1, filmy adhesions that offer no resistance to dissection; 2, fibrous adhesions that are dissectable by hand; 3, fibrous adhesions that are dissectable by blunt instruments; and 4, fibrous adhesions that are dissectable by sharp instruments. The results were as follows, where the extent of adhesions and the tenacity of the adhesions are shown.

Table 12: Efficacy of Polymer in Preventing Adhesions.

Formulation	Number of animals	Extent, %, ± S.D.	Tenacity, 0-4 ± S.D.
6KL	7	0.9 ± 1.7	0.9 ± 0.7
10KL	7	0 ± 0	0 ± 0
20KL	6	4.4 ± 5.0	0.9 ± 0.7
18.5KL t-PA	7	8.9 ± 13.1	1.6 ± 1.3
Control	7	35 ± 22	3.3 ± 0.6

Example 20: Polymerization of Ultrathin layers of Polymer on the surface of blood vessels to reduce thrombosis after vessel injury.

Blood vessels were harvested from rats and were rinsed free of blood. The endothelium of the vessel were removed by inserting a wooden dowel and rotating the vessel over the dowel. One vessel was used as a control, and was exposed to flowing blood as described below without further modification. Another vessel was treated first by exposure to eosin Y at 1 mM in saline, then rinsed in HEPES buffered saline, then filled with a solution of PEG-MA, PEG 10K with acrylate end-capped oligomers of DL lactide, containing triethanolamine (TEA) (100 mM) and N-vinylpyrrolidone (VP) (0.15%) and then illuminated by exposure to an argon ion laser at 0.5 W/cm2 for 15 sec. The nonpolymerized prepolymer mixture in the lumen of the vessel was rinsed away with saline. Human blood was collected from the antecubital vein and was anticoagulated with heparin at 2 units/ml. This blood was perfused through each vessel by a syringe pump at a flow rate corresponding to a wall shear rate of approximately 200/s for 7 min. The vessel was then superficially rinsed in saline and fixed in formaldehyde.

The treated vessel did not appear colored or different in color after perfusion compared to its color before perfusion, while the untreated control vessel appeared blood red. Thin segments of each vessel were cut from each vessel, were mounted on end, and were examined by environmental scanning electron microscopy (ESEM). ESEM is performed on hydrated samples in relatively low vacuum. This permits the visualization of the polymer film coating in the swollen and wet state. This is important to obtain measurements that may be readily interpreted, since the polymer film is approximately 95% water. A high degree of thrombosis was readily observed in the control vessel. The lumen of this vessel was narrowed to less than one-third its diameter pre-perfusion by the accumulation of thrombus, as shown in Figure 6A. By contrast, no thrombus could be observed in the lumen of the treated vessel, as shown in Figure 6B. A higher magnification of the vessel wall demonstrated no adherent thrombus. A still higher magnification shows a white structure which is the polymer film, which is different in contrast from the tissue due to differential charging under the electron beam of the ESEM. The film may be seen to be precisely conformed to the shape of the vessel and be approximately 5 - 8 μm thick.

The region of polymerization was restricted to the neighborhood of the blood vessel wall surface. The photosensitive dye was adsorbed to the vessel wall. Unbound dye was rinsed away. The entire lumen was filled with prepolymer, but upon illumination the gel formation was restricted to the vessel wall where the dye and the prepolymer meet. This interfacial polymerization process can be conducted to produce surface adherent layers that vary in thickness from less than 7 μm to more than 500 μm.

The above procedure was performed in 8 control rat arteries, and 8 treated arteries, with equivalent light microscopic histological results as described above. As demonstrated by this study, PEG prepolymers can be polymerized upon the lumenal surface of blood vessels. The immediate effect of this modification is to reduce the thrombogenicity of an injured blood vessel surface. This has clear utility in improving the outcome of balloon angioplasty by reducing the thrombogenicity of the vessel and lesion injured by balloon dilation. Another effect of this modification is to be reduce smooth muscle cell hyperplasia. This may be expected for two reasons. First, platelets contain a potent growth factor, platelet-derived growth factor (PDGF), thought to be involved in post-angioplasty hyperplasia. The interruption of the delivery of PDGF itself poses a pharmacological intervention, in that a "drug" that would have been delivered by the platelets would be prevented from being delivered. Thrombosis results in the generation of thrombin, which is a known smooth muscle cell mitogen. The interruption of thrombin generation and delivery to the vessel wall also poses a pharmacological intervention. There are other growth factors soluble in plasma which are known to be smooth muscle cell mitogens. The interruption of thrombin generation and delivery to the vessel wall also poses a pharmacological intervention. Moreover, there are other growth factors soluble in plasma which are known to be smooth muscle cell mitogens. The gel layer is known to present a permselective barrier on the surface of the tissue, and thus the gel layer may reasonably be expected to reduce hyperplasia after angioplasty. The inhibition of thrombosis upon the vessel wall may also reduce the incidence of abrupt reclosure and vasospasm, both of which occur sometimes following vascular intervention.

Example 21: Interfacial Polymerization of Macromers Inside Blood Vessels to Prevent Thrombosis.

Macromer solutions were polymerized interfacially within previously injured blood vessels *in vivo* to prevent thrombosis. The carotid artery was exposed, and a polyethylene tube (PE-10) was used to cannulate the exterior carotid artery. The artery was clamped with fine arterial clamps proximal to the interior/exterior carotid artery bifurcation and approximately 2 cm distal to the bifurcation. A 1 ml tuberculin syringe was used to rinse the blood from the lumen of the isolated zone by filling and emptying the vessel zone. The vessel was injured by crushing using a hemostat. The isolated zone was filled with a 10 mM solution of eosin Y for 2 minutes, after which it was rinsed and filled with a 20% solution of a macromer in saline with 0.1 mM triethanolamine and 0.15% N-vinyl pyrrolidinone. The macromer consisted of a PEG chain of MW 8,000 daltons, extended on both sides with a lactic acid oligomer of an average degree of polymerization of 5 lactidyl groups, and further acrylated nominally at both ends by reaction with acryloyl chloride. The vessel was illuminated transmurally using an argon ion laser (514 nm) at an intensity of approximately 1 mW/cm^2 for 5 seconds. Following this, the cannula was removed from the exterior carotid artery and the artery was ligated at the bifurcation. The arterial clamps were removed to permit the resumption of blood flow. Perfusion was allowed for 20 minutes, following which the vessel were again isolated, removed from the body, gently rinsed, fixed, and prepared for light microscopic histological analysis. Using the naked eye, the crushed segments in control animals, which lacked illumination, were red, indicating internal thrombus with entrapped red blood cells. By contrast, no

redness was observed at the site of the crush injury in the treated vessels. Histology showed extensive thrombus, fibrin, and entrapped red blood cells in the non-treated vessels. By contrast, no thrombus or fibrin or entrapped red blood cells were observed in the treated vessels. The procedure was conducted in four control animals and three treated animals.

This example demonstrates that the polymerization can be carried out *in situ* in the living animal, that the polymer coating remains adherent to the vessel wall during arterial blood flow, and that the polymer coating can prevent thrombosis *in vivo* in non-anticoagulated animals. This approach to treatment has clear benefits in preventing abrupt reclosure, vasospasm, and restenosis after intravascular interventional procedures. Moreover, it is more generally applicable to other intraluminal and open-surface organs to be treated.

Modifications and variations of the present invention, the macromer and polymeric compositions and methods of use thereof, will be obvious to those skilled in the art from the foregoing detailed description. Such modifications and variations are intended to come within the scope of the appended claims.

We claim:

1. A biodegradable, polymerizable, and at least substantially water soluble macromer comprising at least one water soluble region, at least one degradable region, and at least two free radical polymerizable regions, wherein the polymerizable regions are separated from each other by at least one degradable region.

2. The macromer of claim 1 wherein the water soluble region is attached to a degradable region, at least one polymerizable region is attached to the water soluble region, and at least one polymerizable region is attached to the degradable region.

3. The macromer of claim 1 wherein the water soluble region forms a central core, at least two degradable regions are attached to the core, and at least two polymerizable regions are attached to the degradable regions.

4. The macromer of claim 2 wherein the degradable region is a central core, at least two water soluble regions are attached to the core, and at least one polymerizable region is attached to each water soluble region.

5. The macromer of claim 1 wherein the water soluble region is a macromer backbone, the degradable region is a branch or graft attached to the macromer backbone, and at least two polymerizable regions are attached to the degradable regions.

6. The macromer of claim 1 wherein the degradable region is a macromer backbone, the water soluble region is a branch or graft attached to the degradable backbone, and two or more polymerizable regions are attached to the water soluble branches or grafts.

7. The macromer of claim 1 wherein the water soluble region is a star backbone, the degradable region is a branch or graft attached to the water

soluble star backbone, and at least two polymerizable regions are attached to a degradable branch or graft.

8. The macromer of claim 1 wherein the degradable region is a star backbone, the water soluble region is a branch or graft attached to the degradable star backbone, and two or more polymerizable regions are attached to the water soluble branch or graft.

9. The macromer of claim 1 wherein the water soluble region is also the degradable region and two or more polymerizable regions are attached to the water soluble regions.

10. The macromer of claim 1 wherein the water soluble region is also the degradable region, one or more additional degradable regions are grafts or branches upon the water soluble region, and a total of two or more polymerizable regions are attached to the degradable regions.

11. The macromer of claim 1 comprising a core, at least two extensions on the core, and an end cap on at least two extensions, wherein

the core comprises poly(ethylene glycol).

12. The macromer of claim 11 wherein

each extension comprises biodegradable poly(hydroxy acid); and

each end cap comprises an acrylate oligomer or monomer.

13. The macromer of claim 12 wherein the poly(ethylene glycol) has a molecular weight between about 400 and 30,000 Da;

the poly(hydroxy acid) oligomers have a molecular weight between about 200 and 1200 Da; and

the acrylate oligomer or monomer have a molecular weight between about 50 and 200 Da.

14. The macromer of claim 1 wherein the polymerizable regions contain a carbon-carbon double

bond capable of cross-linking and polymerizing macromers.

15. The macromer of claim 1 wherein crosslinking and polymerization of the macromer are initiated by a light-sensitive free-radical polymerization initiator with or without a cocatalyst, further comprising a free radical polymerization initiator.

16. The macromer of claim 15 wherein the initiator is selected from the group consisting of xanthine dyes, acridine dyes, thiazine dyes, phenazine dyes, camphorquinone dyes, and acetophenone dyes.

17. The macromer of claim 16 wherein the initiator is selected from the group consisting of an eosin dye with triethanolamine, 2,2-dimethyl-2-phenyl acetophenone, and 2-methoxy-2-phenyl acetophenone.

18. The macromer of claim 1 wherein crosslinking or polymerizations are initiated *in situ* by light having a wavelength of 320 nm or longer.

19. The macromer of claim 1 wherein the degradable region is selected from the group consisting of poly (hydroxy acids), poly(lactones), poly(amino acids), poly(anhydrides), poly(orthoesters), poly(phosphazines), and poly(phosphoesters).

20. The macromer of claim 19 wherein the degradable region is a poly(α-hydroxy acid) selected from the group consisting of poly(glycolic acid), poly(DL-lactic acid) and poly(L-lactic acid).

21. The macromer of claim 19 wherein the poly(lactone) is selected from the group consisting of poly(ε-caprolactone), poly (δ-valerolactone) or poly(λ-butyrolactone).

22. The macromer of claim 1 wherein the water soluble region is selected from the group consisting of poly(ethylene glycol), poly(ethylene oxide), poly(vinyl alcohol), poly(vinylpyrrolidone),

poly(ethyloxazoline), poly(ethylene oxide)-co-poly(propyleneoxide) block copolymers, polysaccharides, carbohydrates, proteins, and combinations thereof.

23. The macromer of claim 1 further comprising biologically active molecules selected from the group consisting of proteins, carbohydrates, nucleic acids, organic molecules, inorganic biologically active molecules, cells, tissues, and tissue aggregates.

24. A method of forming a polymeric, biocompatible material on tissue comprising

applying to the tissue a solution of biodegradable, polymerizable, and at least substantially water soluble macromer comprising at least one water soluble region, at least one degradable region, and at least two free radical polymerizable regions, wherein the polymerizable regions are separated from each other by at least one degradable region, in the presence of a free radical initiator, and polymerizing the macromer.

25. The method of claim 24 wherein the tissue is coated to prevent adhesion of the tissue to other tissue.

26. The method of claim 24 wherein the tissue is coated and adhered to other tissue during polymerization.

27. The method of claim 24 further comprising providing with the macromer solution biologically active molecules selected from the group consisting of proteins, carbohydrates, nucleic acids, organic molecules, inorganic biologically active molecules, cells, tissues, and tissue aggregates.

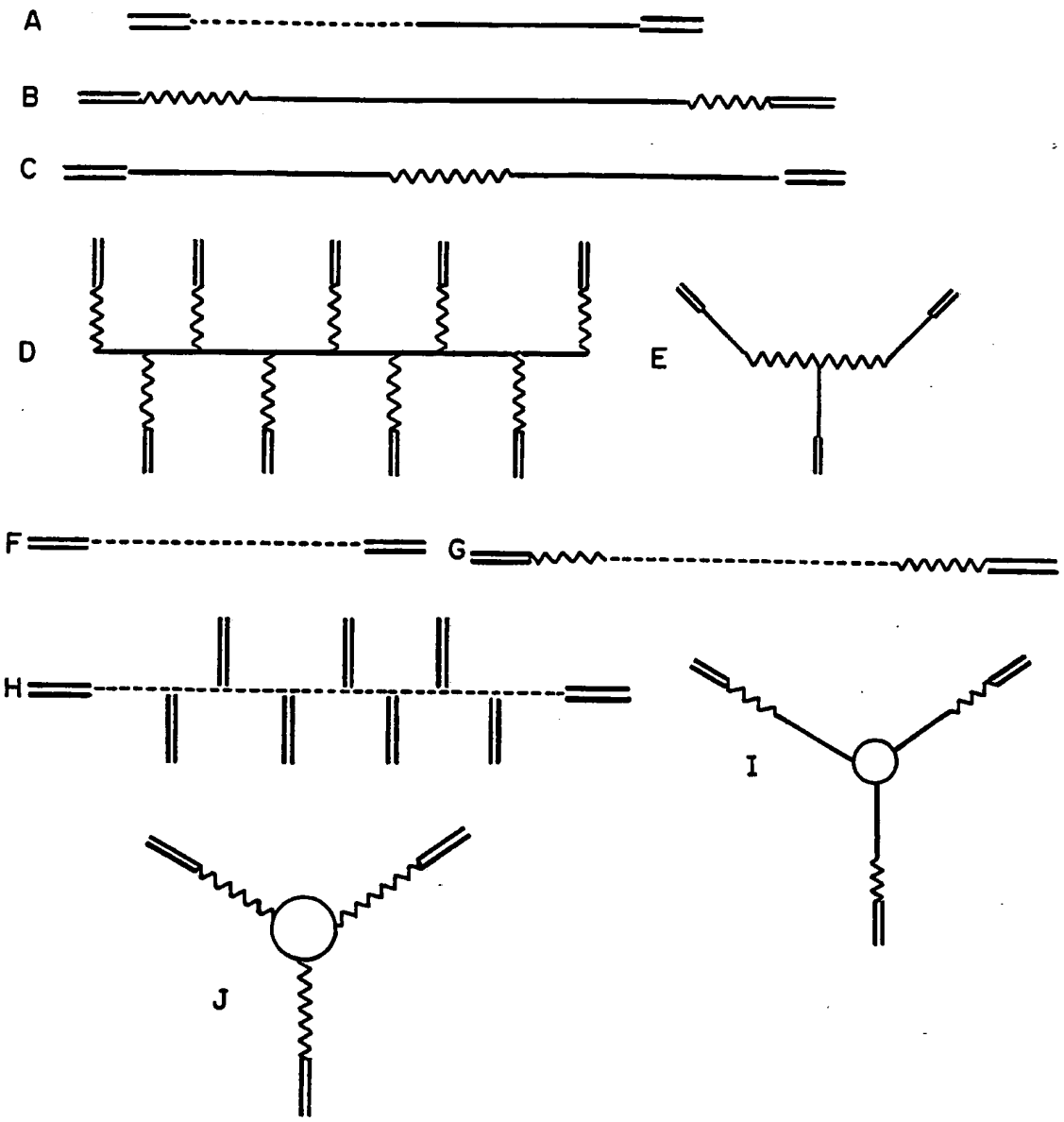
28. The method of claim 24 further comprising first applying a free radical initiator at the site where the macromer solution is to be polymerized.

29. The method of claim 28 wherein the initiator binds to the tissue, further comprising

removing unbound initiator prior to application of the macromer solution.

30. A method for controlled release of biologically active molecules comprising mixing biologically active molecules with a solution of biodegradable, polymerizable, and at least substantially water soluble macromer comprising at least one water soluble region, at least one degradable region, and at least two free radical polymerizable regions, wherein the polymerizable regions are separated from each other by at least one degradable region, in the presence of a free radical initiator, and polymerizing the macromer to entrap the molecules within the resulting polymer.

31. The method of claim 30 wherein the polymer forms a shape selected from the group consisting of microspheres, sheets, rods, and particles.



- WATER SOLUBLE COMPONENT

- HYDROLIZABLE COMPONENT

- WATER SOLUBLE AND HYDROLIZABLE COMPONENT

- PHOTOPOLYMERIZABLE COMPONENT

FIG. 1

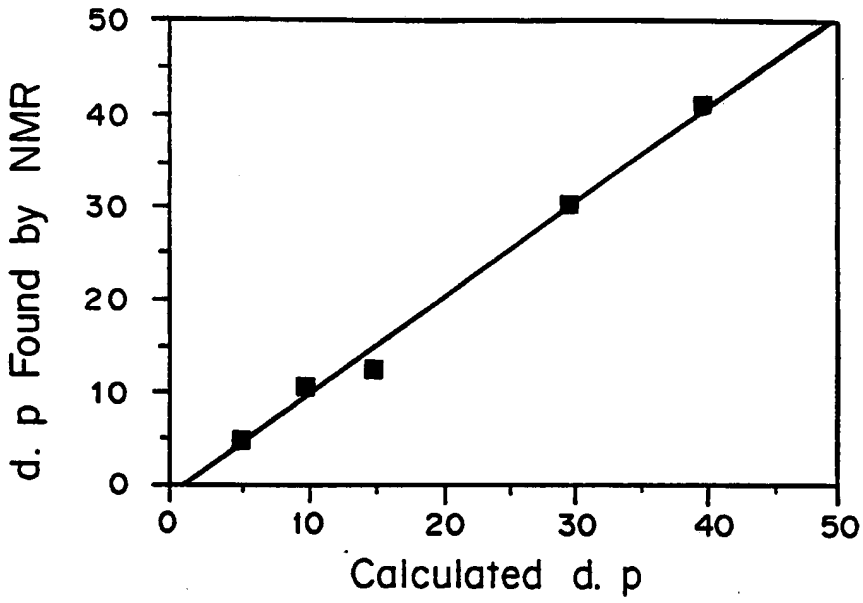


FIG. 1a

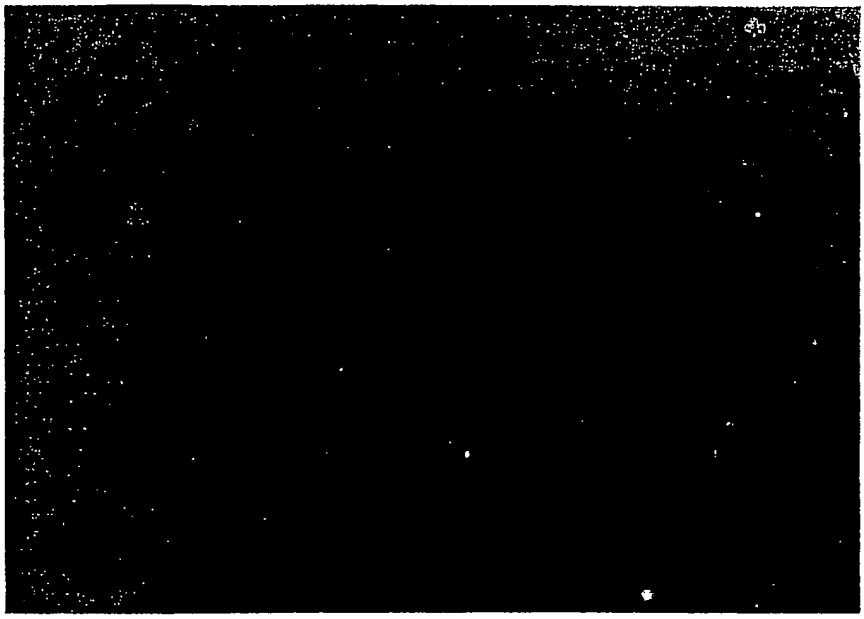


FIG. 2a

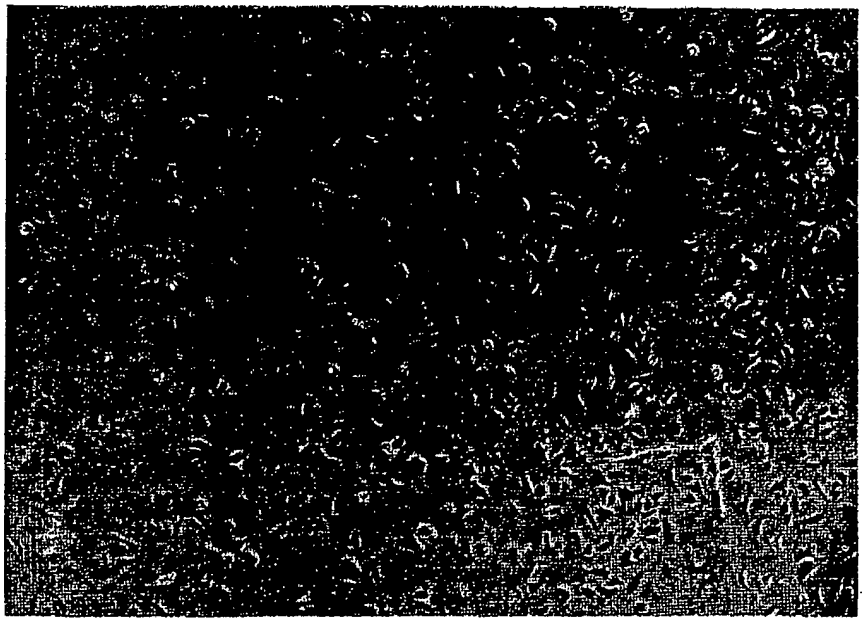


FIG. 2b

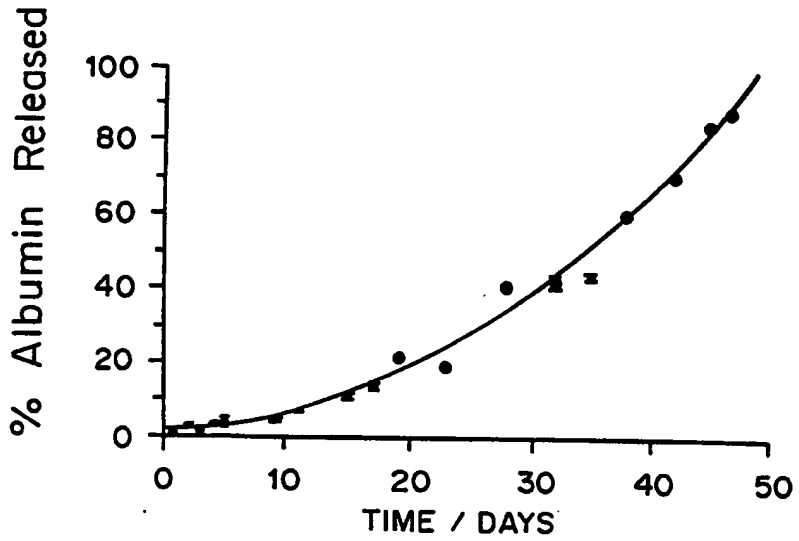

% Albumin Released
100
80
60
40
20
0
0
10
20
30
40
50
TIME / DAYS

FIG. 3a

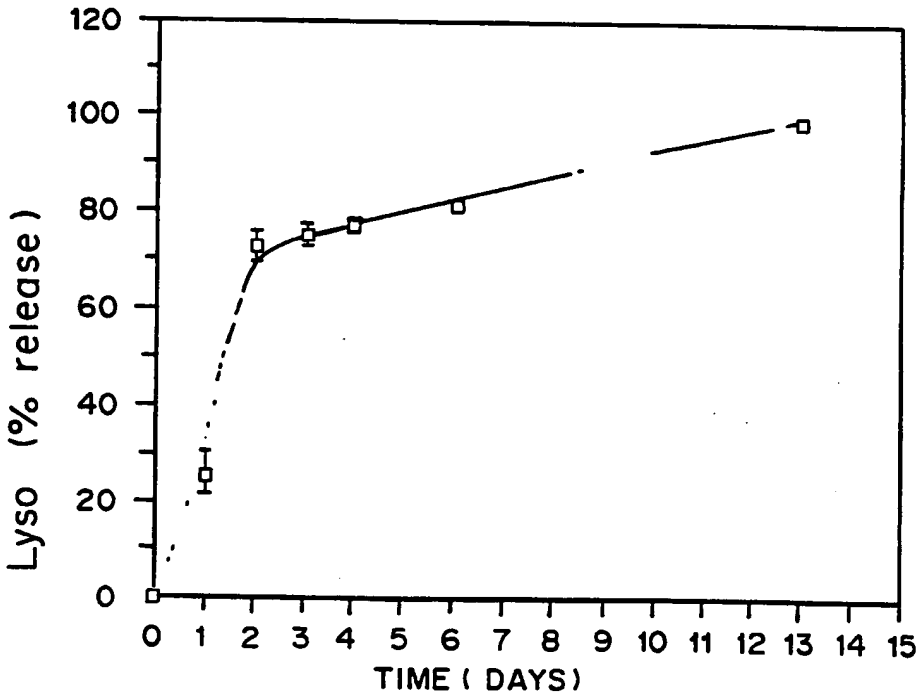
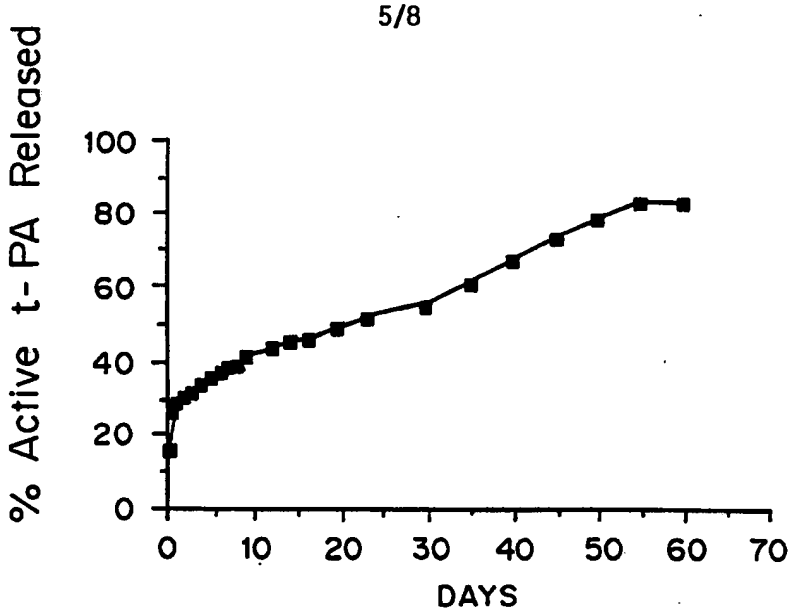

Lyso (% release)
120
100
80
60
40
20
0
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15
TIME (DAYS)

FIG. 3b


% Active t-PA Released
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80
60
40
20
0
0
10
20
30
40
50
60
70
DAYS

FIG. 4a

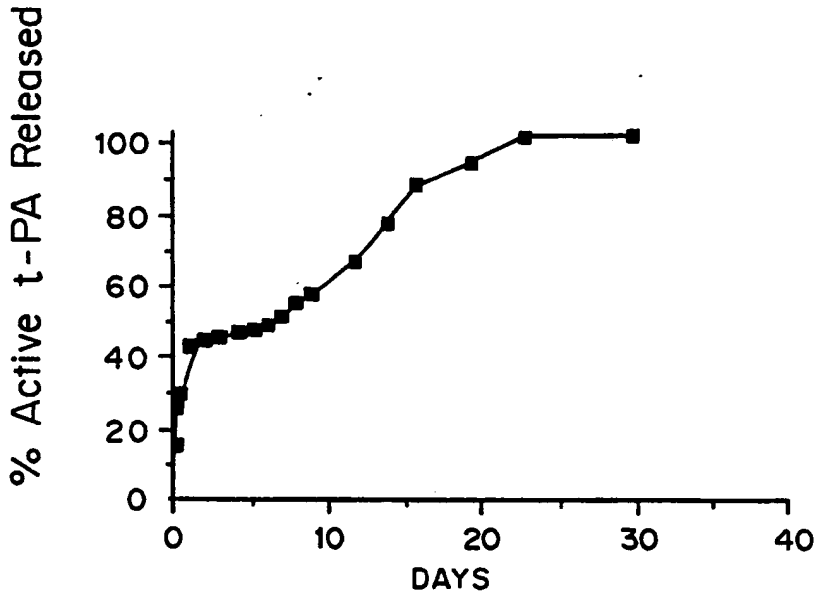
% Active t-PA Released
100
80
60
40
20
0
0
10
20
30
40
DAYS

FIG. 4b

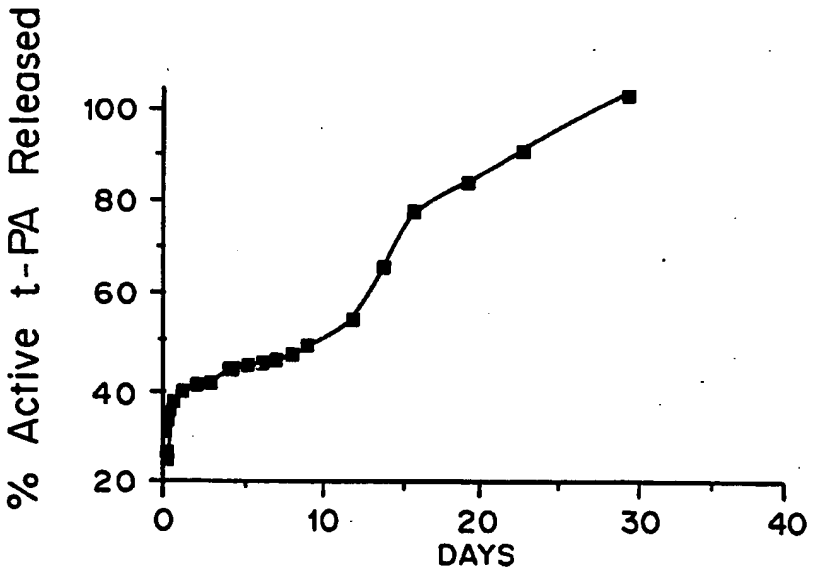

FIG. 4c

FIG. 5a

FIG. 5b

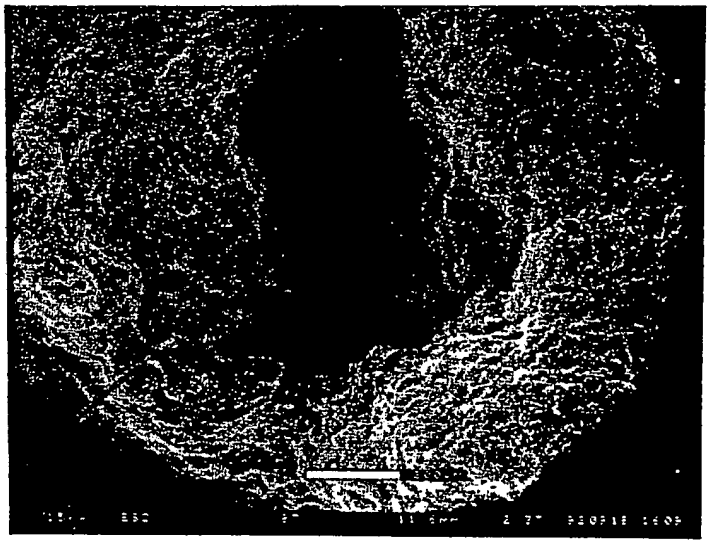

FIG. 6a

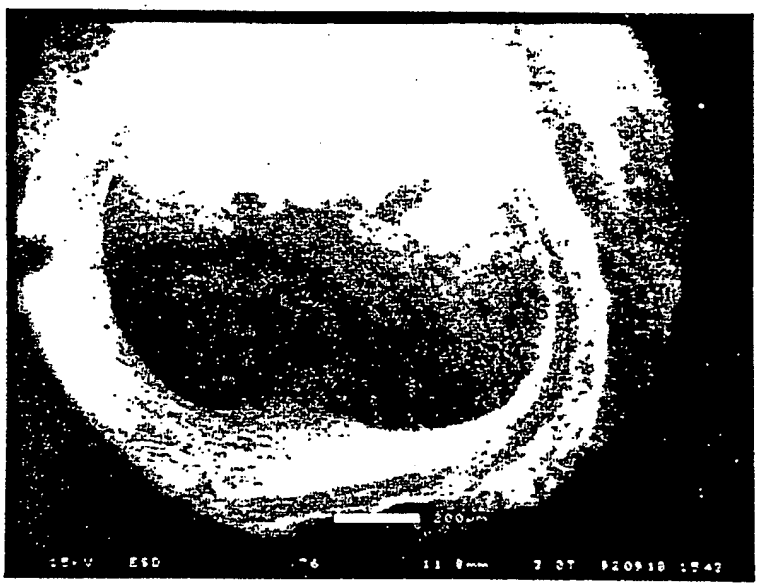

FIG. 6b

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US93/01773

A. CLASSIFICATION OF SUBJECT MATTER

IPC(5) :A61K 9/50
US CL :522/26, 43, 56, 68, 87, 88, 149, 171, 181; 424/423, 426, 489
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 522/26, 43, 56, 68, 87, 88, 149, 171, 181; 424/423, 426, 489

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US, A, 4,310,397 (KAETSU ET AL) 12 JANUARY 1982. See entire document.	1-31
A	US, A, 4,994,277 (HIGHAM ET AL.) 19 FEBRUARY 1991. See entire document.	24-31
A,P	US, A, 5,135,751 (HENRY ET AL.) 04 AUGUST 1992. See entire document.	24-31
A,P	US, A, 5,108,755 (DANIELS ET AL.) 28 APRIL 1992. See entire document.	24-31
A	US, A, 4,999,417 (DOMB) 12 MARCH 1991 See entire document.	24-31

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
04 APRIL 1993	02 AUG 1993
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231	Authorized officer AMY HULINA
Facsimile No. NOT APPLICABLE	Telephone No. (703) 308-2351

Form PCT/ISA/210 (second sheet)(July 1992)*

INTERNATIONAL SEARCH REPORT

International Application No.
PCT/US93/01773

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US, A, 4,512,910 (SCHMIDLE) 23 APRIL 1985 See entire document.	1-23
A	US, A, 4,533,445 (ORIO) 06 AUGUST 1985 See entire document.	1-23

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